ONE AND TWO-ELECTRON CYCLIZATIONS OF PI-BONDS

By

YONGPING XIE

A DISSERTATION PRESENTED TO THE GRADUATE SCHOOL
OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR THE DEGREE OF
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This dissertation is dedicated to my parents

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I thank the Department of Chemistry at the University of Florida, the members of my committee and all who helped with the completion of this research.

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Abstract of Dissertation Presented to the Graduate School of the University of Florida in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy

ONE AND TWO- ELECTRON CYCLIZATIONS OF PI-BONDS

By

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Chairman: J. Eric Enholm
Major Department: Chemistry

This dissertation investigated the intramolecular ring formation between alkenes, carbonyls, and other π-bonds in a one- and two-electron process.

The first area of study included a synthetic approach towards the C44 to C54 portion of the antitumor natural compound halichondrin B by an enantiospecific route. After a 28 step synthesis, an α,β-unsaturated ester was obtained which was studied as a substrate for a Moffat-type Wittig-Michael cyclization reaction. Furthermore, a great deal of important synthetic methodology on heterocycles is discussed.

The second area of study investigated the reactivity of intramolecular cyclizations promoted by a tin ketyl. Under mild and neutral free radical conditions, an α,β-unsaturated ketone reacted selectively, in the presence of an aldehyde, with tributyltin hydride to produce a resonance-stabilized

allylic O-stannyl ketyl. Upon subsequent hydrogen atom abstraction, a tin enolate was afforded which participated in an intramolecular directed aldol reaction. Although substrates with two carbonyls can lead to several possible aldol products, only a single product was obtained. Up to three new stereocenters resulted in the annulated bicyclic alcohols in a highly stereoselective manner, as determined by single crystal x-ray analysis. The reaction represented a very mild alternative to metal enolate formation which usually requires strong hindered bases such as LDA or strongly reductive dissolving metal conditions to achieve success.

The third area of study investigated the possibility of intramolecular radical S_{N}' elimination reactions. Allylic phenyl sulfone (or sulfide) and aldehyde parters were examined under the radical reaction conditions. The studies showed that a tin ketyl abstracts a hydrogen faster than it adds to double bond to promote an S_{N}' elimination reaction.

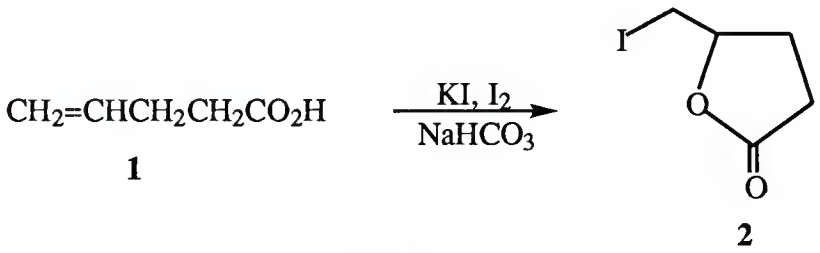
CHAPTER 1

INTRODUCTION

Many biologically interesting molecules, such as polyether antibiotics and lactones, have 5- and 6-membered heterocyclic rings.[1] The structural complexity and biological activity of these compounds have stimulated considerable interest in their synthesis, especially, in the formation of their ring system. Among the many cyclization methods, ring-formation by functionalization of a double bond is one of the most used reactions in organic synthesis.[2] Since Bougault reported and developed the conversion of β,γ- or δ,γ-unsaturated acids into iodolactones, a lot of related and interesting methods have been exploited, showing the utility of this new synthetic tool.[3]

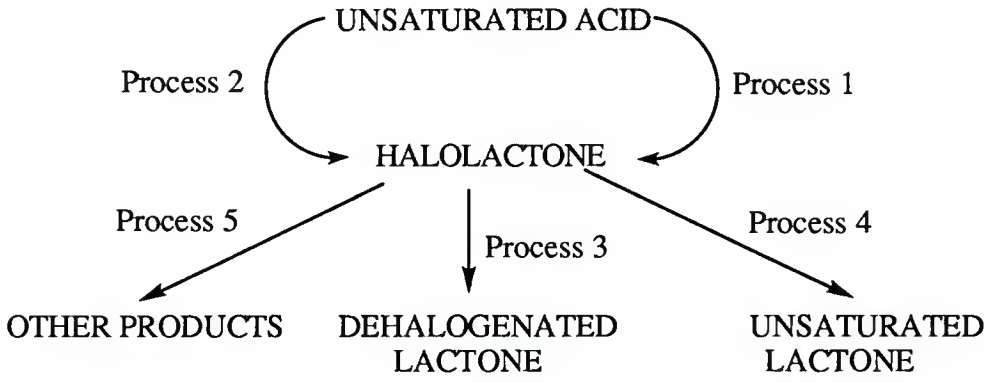
His basic procedure, now referred to as halolactonization, was to dissolve the unsaturated acid in aqueous sodium bicarbonate, and next treat it with a solution of iodine in aqueous potassium iodide; the iodolactone would separate from the reaction medium.[3] The conversion of δ,γ-pentenoic acid (1) into the γ-iodolactone 2 is a simple example (Scheme 1-1). The accepted mechanism involves attack by positive halogen on the double bond of the unsaturated acid which affords a halonium

ion which then undergoes intramolecular displacement by the carboxylate anion to give halolactone product.[4]



Scheme 1-1

Dowle and Davies reviewed the uses of halolactonization and its application as a synthetic tool in organic chemistry (Scheme 1-2):[5]



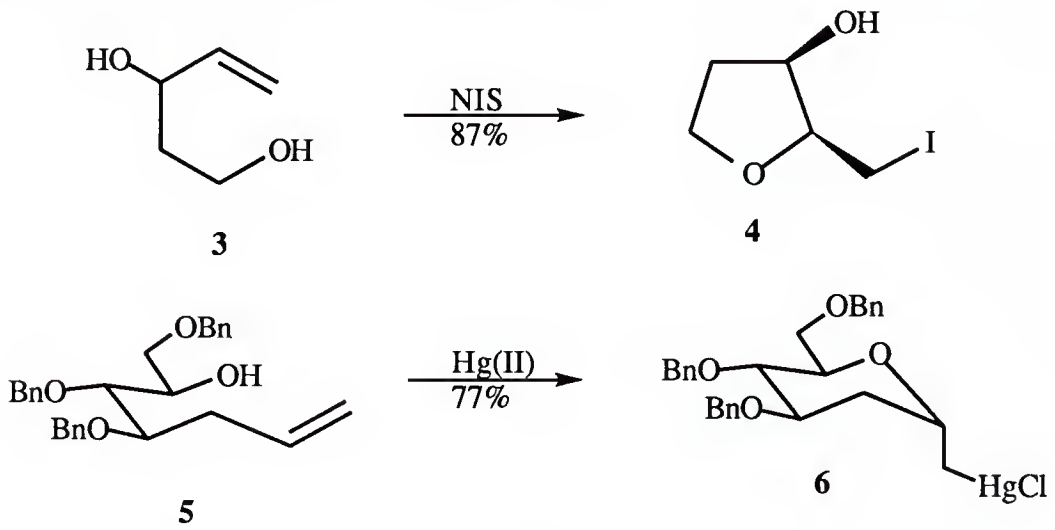
Scheme 1-2

Processes 3 and 4 are of particular value in syntheses. In Kishi's first total synthesis of halichondrins, vitamin D_2, and vitamin D_3, unsaturated acids were subjected to iodolactonizations, followed by reductive removal of the iodine with tri-n-butyltin hydride. This gave γ–lactones which are very important intermediates of the syntheses.[6,7] The dehydrohalogenation of halolactones (Process 4) with diazabicycloundecane (DBU) or diazabicyclononene (DBN) can

render unsaturated lactones to form intermediates of natural products.[8]

Recently, a variety of investigations on the factors affecting the stereochemistry of ring formation has been carried out. The kinetic ($I_2/NaHCO_3/H_2O/CHCl_3$) or thermodynamic (I_2/MeCN) conditions used in the reaction can determine the high stereoselectivity towards *cis*- or *trans*-iodolactones.[9] The substituents of starting compound and the E or Z configuration of the double bond can also strongly influence the stereochemistry.[10]

Tetrahydrofurans and tetrahydropyrans can be formed from the starting materials containing unsaturated hydroxy groups in a haloetherification reaction (Scheme 1-3). The reagents

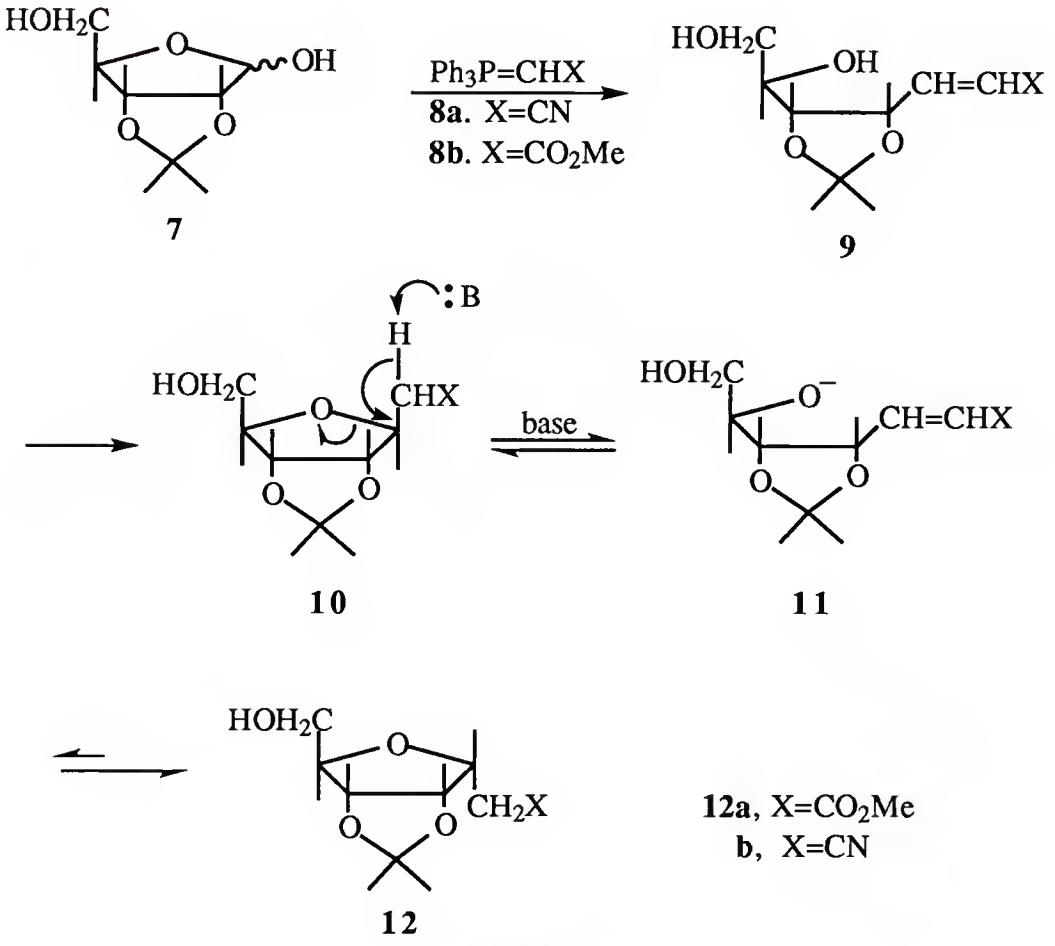


Scheme 1-3

$I_2/NaHCO_3$, Hg(OAc)2, PhSeCl, NIS and TI(III) have all induced the ring formation.[11]

Moffatt and coworkers found that reactions of 2,3-O-isopropylidene-D-ribose (7) with the stablized ylides 8a and

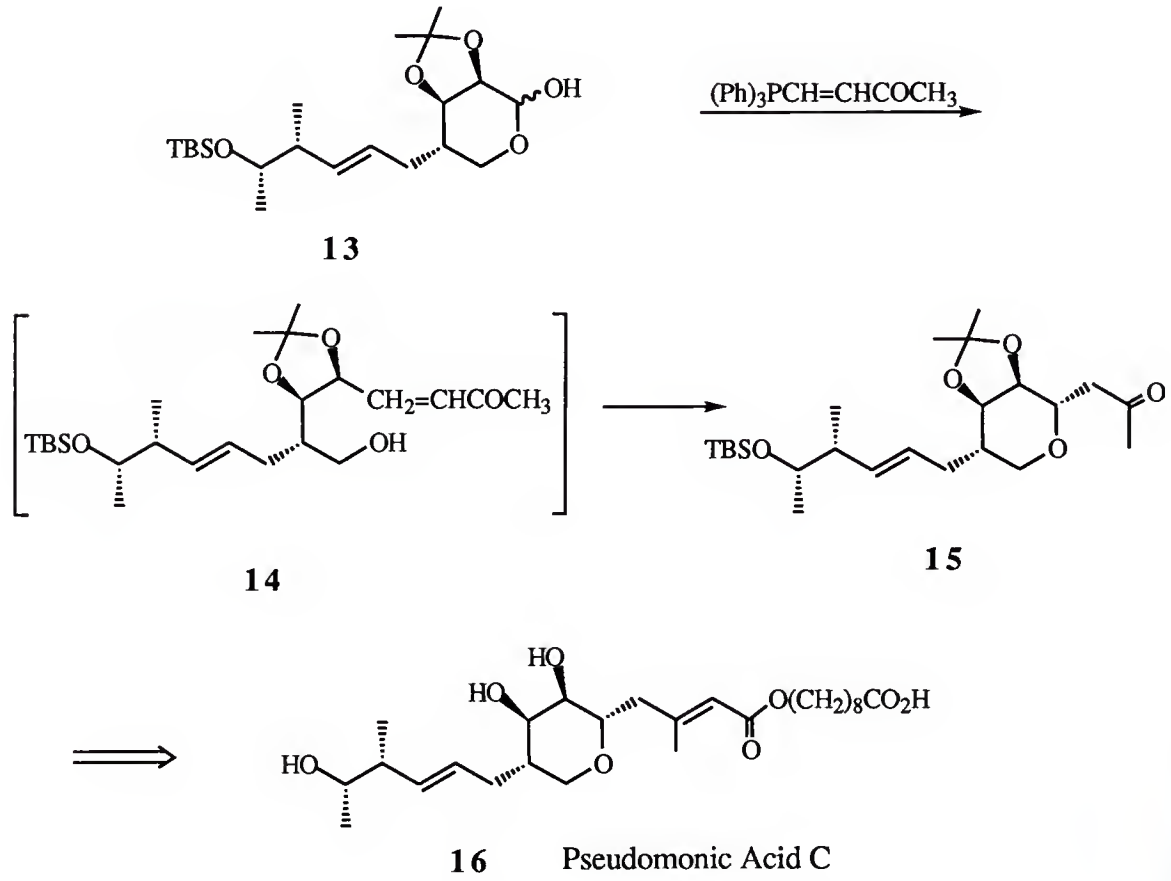
8b in acetonitrile under reflux had undergone a spontaneous, Michael-type, ring closure of 9 to give furanose C-glycoside



Scheme 1-4

10 as a major compound.[12] If, however, the compound 10 was treated with methanolic sodium methoxide in methanol and benzene, isomer 12 predominated. This observation suggested that isomer 10 was the kinetic product and base-catalyzed equilibration of 10 led to a gradual conversion to the more thermodynamically stable isomer 12. A variety of biologically important natural products have been synthesized using this Moffatt-type reaction. For example, Aicher et al.[6c], Kim and

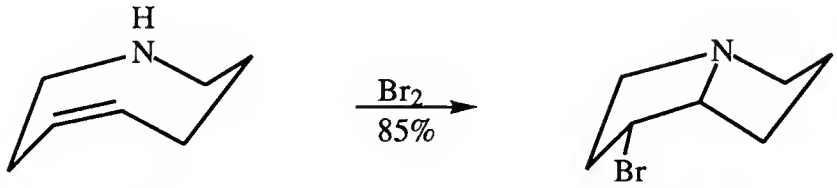
Salomon[6f] synthesized halichondrins; Keck, Kanchensky and Enholm[13] synthesized pseudomonic acid C (Scheme 1-5) using the Moffat-type reaction.



Scheme 1-5

The synthesis of heterocycles containing nitrogen is also possible if proper starting substrates are used. The direct intramolecular cyclization of amines and double bonds has rarely been employed owing to difficulties connected with this kind of reaction. A synthesis of the bicyclic ring system of the pyrrolizidine alkaloids resulted in the stereospecific formation of substituted pyrrolizine 18 *via* a trans-annular cyclization. The reaction gives good yields of

the cyclized products with various electrophiles, such as Br_2, $HgCl_2$ and PhSBr[14] (Scheme 1-6).

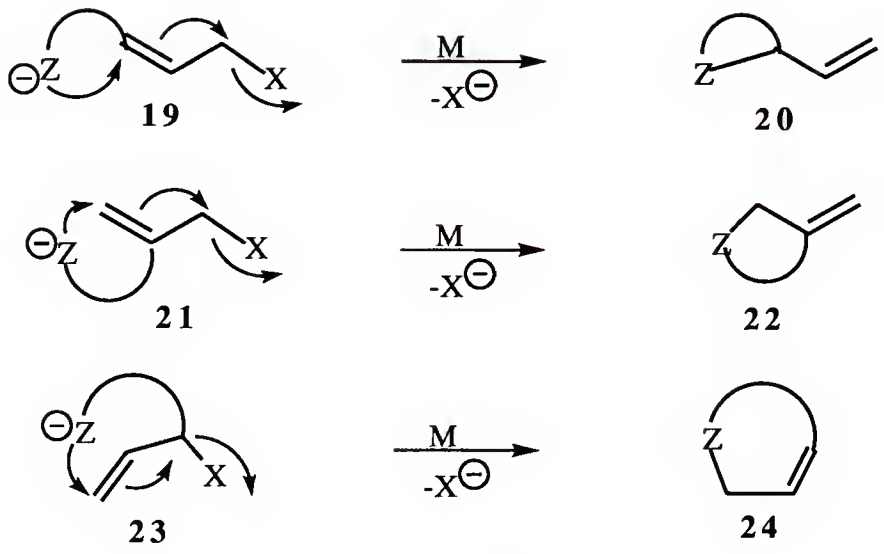


17 18

Scheme 1-6

Furthermore, if oxygen- or nitrogen-centered anions attack upon an allylic system bearing a leaving group, an intramolecular S_N' process may occur to form heterocyclic compounds. There are three types of anionic β-elimination pathways which are relevant to these studies, summarized in Scheme 1-7.[15,16] In the intramolecular verson, the heteroatom (Z) is tethered to the allylic function at several sites[16] (Scheme 1-7). While the most common S_N' transformation is exo-trig depicted as 19 →20, it is worth noting that no examples of 23→24, with the leaving group part of the tether, have been successful without additional structural features. Common leaving groups here include a wide variety of epoxides, mesylates, tosylates and halides, to mention a few.

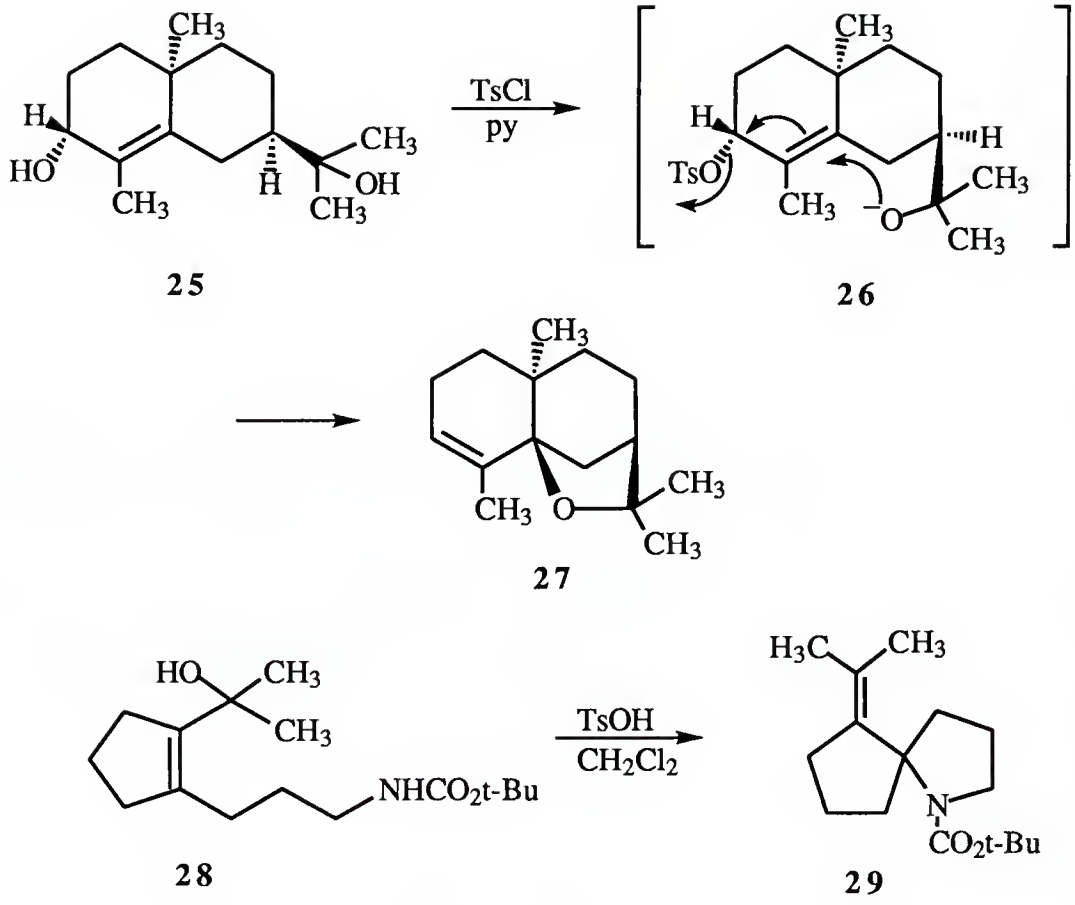
The bond-formation and bond-breaking sequence in S_N' reactions can be regarded as a tandem addition and elimination. At present evidence, it is not clear if it is stepwise or concerted, but the preferred syn-stereochemistry of most S_N' reactions suggests that addition is probably



Scheme 1-7

dependent on the release of the leaving group in the same transition state.[17] There are hundreds of examples of intermolecular anionic S_N' eliminations, but unfortunately, far less is known about the intramolecular version. Only a total of about 50 examples are known and more than half of these reactions exist in fairly recent literature since 1980.[15]

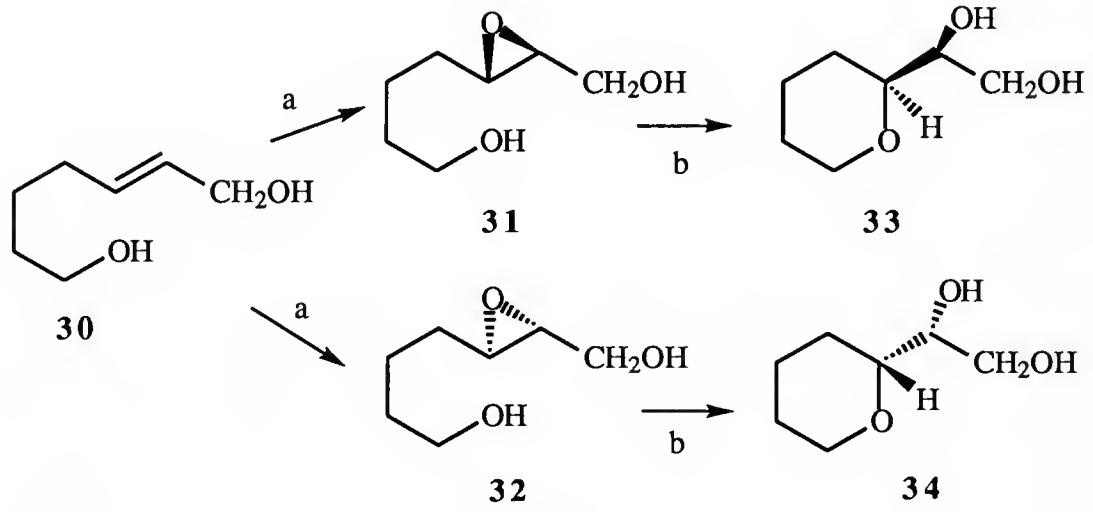
Although the hardness and sometimes variable nucleophilic properties of alkoxide ions can prove to be a disadvantageous synthetic utility, these factors can be overcome if the leaving group is suitable. For instance, regioselective monotosylation of diol 25 leads directly to α-agarofuran.[18] The anti-relationship between the leaving group and the alkoxide facilitates the reaction. Carbinol 28 follows an S_N' 5-exo-trig cyclization in the presence of catalytic p-toluenesulfonic acid in dichloromethane at room temperature (Scheme 1-8).[19]



Scheme 1-8

Another very important methodology to obtain polyfunctionalized tetrahydrofurans and tetrahydropyrans is by epoxidation of an olefin, followed by ring closure with catalytic amount of camphorsulfonic acid (CSA). If a subsequent Sharpless asymmetric epoxidation is applied, the ring closure can create two chiral centers. As shown in Scheme 1-9, the (+) or (-) tartrate ester can produce two enantiomers from same compound, followed by S_N' type ring closure to provide diols 33 and 34, both of which have two chiral centers. Using this methodology, Nicolaou et al.[20] and

Cywin et al.[21] recently synthesized hemibrevetoxin B and antibiotic zincophorin.



(a) Sparpless epoxidation (b) CSA, CH_2Cl_2

Scheme 1-9

Chapter 2 of this dissertation investigated a synthetic approach towards the C44 to C54 portions of Halichondrin B by an enantiospecific route that is shorter and more accessible than the only currently available synthesis.[6e,6f] The proposed highly convergent synthesis utilized two "subunits" constructed in 10-13 steps that arise from carbohydrates and asymmetric epoxidation technology. Key steps in the route that lead to great simplification include (1) an application of a Moffat-type Wittig-Michael cyclization reaction using unsaturated ester as substrate, (2) two different free radical deoxygenations of a carbohydrate, (3) regio- and stereoselective addition of a methyl group (trimethylaluminium) to a Sharpless epoxide

precursor, (4) the formation of the stablized ylide by an acyl imidazolide.

Chapter 3 of this dissertation will show aldol cyclizations initiated by free radicals. A free-radical reaction is a chemical process in which molecules having unpaired electrons are involved. Part of this dissertation will focus on the ring formation between a special type of free radical and double bonds. This general type of reaction has become important in organic synthesis. Most radical cyclizations involve double or triple bonds on various substituents.[22] A simple alkyl substituted carbon centered radical may be considered to be essentially nucleophilic in character because of the inductive effect of the alkyl groups; in contrast, the trifluoromethyl radical is an electrophilic.

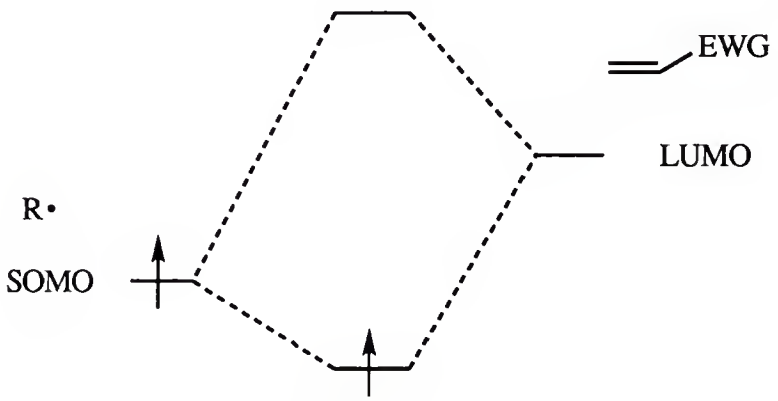


Figure 1-1

Orbital interaction between nucleophilic radical and electron-poor alkene

Giese and Kretzschmar noted that the substituents on the radical or on the alkene may affect the rate of addition.[23]

These results can be described by simplified frontier molecular orbital theory.[23,24]

The singly occupied molecular orbital (SOMO) of the radical selects either the lowest unoccupied molecular orbital (LUMO) (Figure 1-1) or the highest occupied molecular orbital (HOMO) (Figure 1-2) of the alkene system.

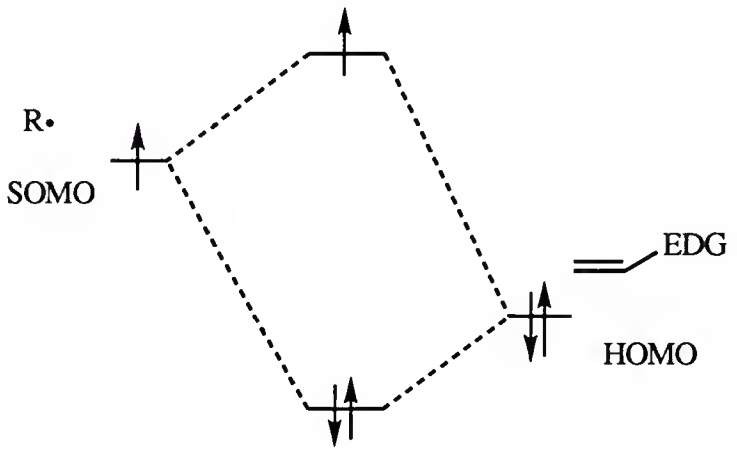


Figure 1-2

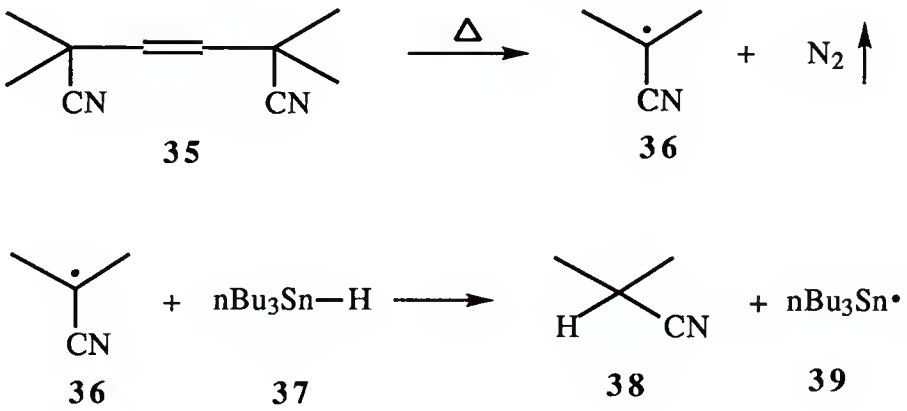
Orbital interaction between electrophilic radical and electron-rich alkene

Electrophilic radicals have SOMO energies which are so low that interaction with the HOMO of the electron rich alkene is dominant, whereas the effect of an electron withdrawing substituent on the olefin is to reduce the LUMO energy to such an extent that this reaction becomes favored for nucleophilic radicals.

Unlike cationic intramolecular cyclizations which provide six-membered rings, five-membered rings are dominant in radical cyclizations through a highly regioselective process.[23a] With various substituted 5-hexenyl radicals, the Beckwith group has carried out a series of elegant

investigations on radical ring formation.[25] The cyclizations prefer a strain-free chair-like transition state, selecting for substituents in pseudoequatorial positions on the ring.

Although there are many methods to provide free radicals, the combination of tributyltin hydride (TBTH) and azobisisobutylnitrile (AIBN) is the most popular and classical method in radical reactions.[26] The thermal decomposition of AIBN produces cyanoisopropyl radicals 36, which are usually not reactive enough to abstract a substrate's hydrogens, but are capable of abstracting a hydrogen atom from the weak Sn-H bond of tributyltin hydride (TBTH) 37 to give the designed tributyltin radical 39.[26] (Scheme 1-10)

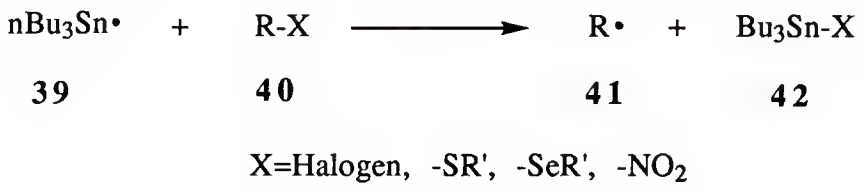


Scheme 1-10

TBTH is commercially available or it can be readily prepared.[27] For more than twenty years the utilization of TBTH in the free radical area has stimulated more and more synthetic organic chemists to study new cyclization methods.[28-29] Free radicals were thought to be unruly and

relegated to the area of polymer chemistry.[30] New information on many kinds of radicals, their properties and use in organic synthesis has simply erupted in publications. More and more complex molecules have been synthesized by the radical reactions from worldwide research groups.[23,29] There are advantages of free radicals over ions in organic synthesis.[26] Neutral and mild reaction conditions contrast the harsh reactions of cations or anions. Solvation effects are much less important in neutral free radical reactions. Radical reactions do not necessarily need protecting groups. Additionally, the regio-, stereo- and chemoselectivities of some free radical reactions are high and predictable.

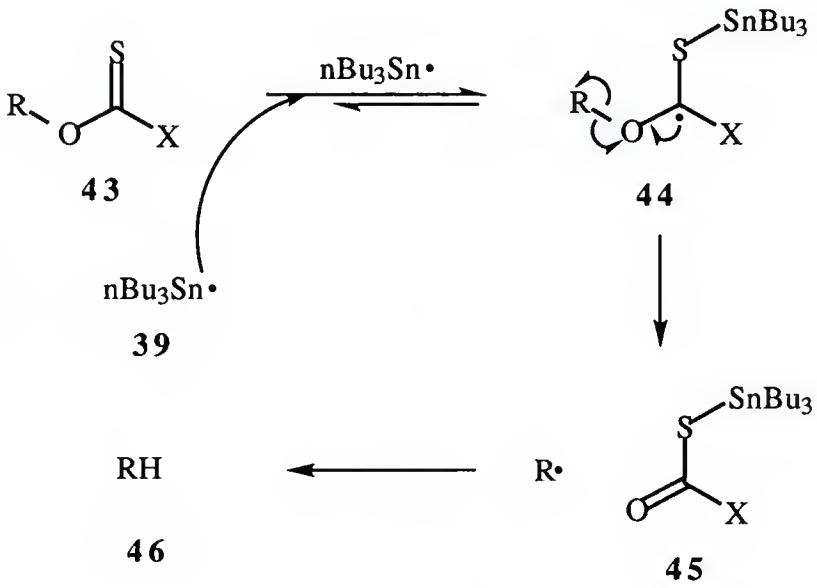
There are two broad classes of free radical reactions: atom or group abstraction (Scheme 1-11) and addition to multiple bonds.[29e]



Scheme 1-11

Deoxygenation reactions by traditional ionic displacement of a suitable sulphonate ester with lithium aluminium hydride are often sluggish or unsuccessful with carbohydrates. Barton and McCombie's research on sulfur-related deoxygenation methodology has led to one of the most useful radical reactions in organic synthesis.[26,31,32]

As shown in Scheme 1-12, the reaction is believed to proceed via reversible addition of the organostannyl radical to the thiocarbonyl group followed by fragmentation of the intermediate carbon centered radical to give a carbonyl group with concomitant liberation of the derived alkyl radicals R•.



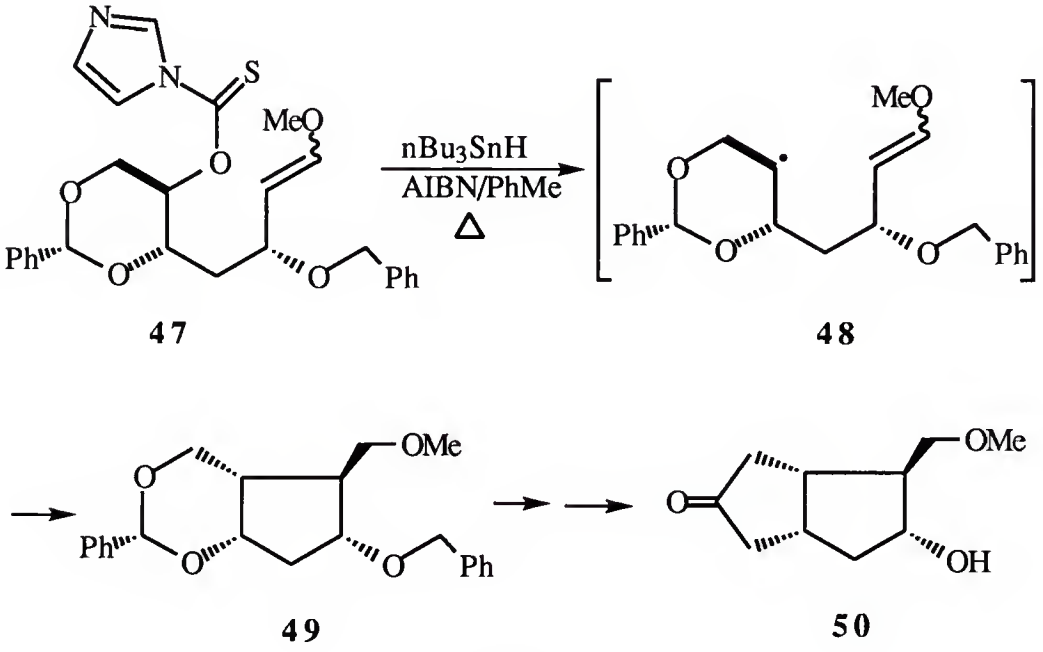
X=SMe, Ph, OPh, OC_6F_5, SPh

Scheme 1-12

The hydroxy compounds include primary, secondary, tertiary and diols. We will use this methodology in total synthesis of halicondrin B. The radical intermediate produced by this method can also undergo further intramolecular cyclization through a chair-like transition state (Scheme 1-13).

Corey lactone 50, an important drug precursor, was prepared by alkyl radical 48 which was formed by the fragmentation of the thiocarboxylate using Barton's method as a key step, followed by radical addition on double bond to obtain the desired five-membered ring system with high

steroselectivities (Scheme 1-13).[33] The main criticism regarding radical chemistry has been that a carbon centered free radical is a planar entity and hence high stereoselection is impossible in carbon-carbon bond forming reactions. Motherwell (page 15) rebuffs this argument by saying that "the planarity of enolate anions, iminium ions and even free carbocations has not hindered the effective operation of stereoelectronic control elements leading to stereospecific reactions."[26]



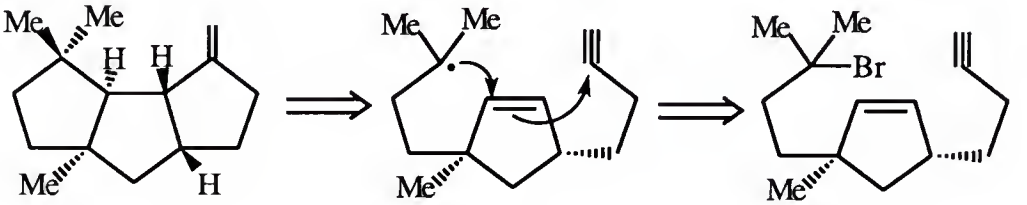
47 48 49 50

Scheme 1-13

Both linear and angular triquinane natural product skeletons have been constructed by tandem radical cyclizations in a key step.[29e,f] An example of tandem sequence started with the generation of a 5-hexenyl radical from tertiary bromide 53.[34] This was captured by the olefin and finally terminated by addition to a suitably disposed

alkyne. This demonstrates evidence that sometimes free radical cyclization reactions can give an easy solution to a complex natural product synthesis.

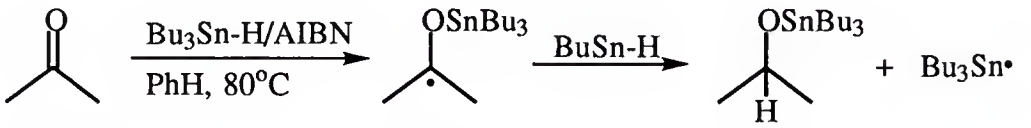
The second part of this dissertation will focus on intramolecular cyclizations by free radicals generated from ketone carbonyls. When TBTH reacts with several carbonyl



51 52 53

Scheme 1-14

functions in polar solvents under Lewis acid catalysis , TBTH donates a hydride (H^-) to carbonyl carbon center to give a tin alkoxide. Conversely, a free radical pathway can also occur with nonpolar solvents, AIBN, and heat (Scheme 1-15).[29a] The tributyltin radical adds to the oxygen atom of the carbon-oxygen double bond 54 to form O-stannyl ketyl 55.



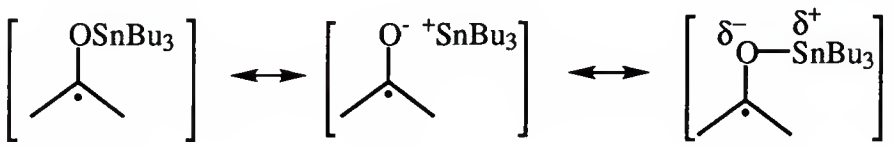
54 55 56

Scheme 1-15

This carbon-centered radical can engage in a variety of additional reactions, or it can abstract a hydrogen atom (H·) to provide the tin alkoxide species 56 and the tributyltin

radical can now repeat the process. The free alcohol is obtained when the tin alkoxide is quenched with water.

The tin ketyl can be regarded as a pseudo-protected radical anion, where the O-Sn bond has a certain degree of ionic character due to electronegativity differences (Scheme 1-16) between oxygen and tin. The apparent challenge to synthetic chemists is to investigate both radical and anionic elements of reactivity which are presented by this species.

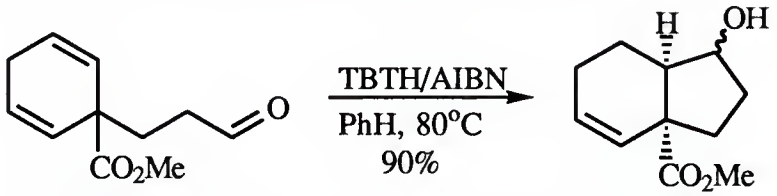


55 57 58

Scheme 1-16

Prior to Enholm's studies, very few papers on the coupling of ketones (or aldehyde) and olefins were reported.[39,40,41] From nonreagent based methods, both photochemical and electrochemical approachs can produce a ketyl radical anion.[35,36] As early as 1986, Beckwith and Roberts gave the first example (Scheme 1-17) of an aldehyde coupled to an olefin with TBTH to assemble a bicyclic system.[37] The reaction undoubtedly involves ring closure of a tin ketyl. Although the yield was excellent, they found that the reaction was slow and required additional TBTH and AIBN to go to completion. They thought that the formation of the radical was rapidly reversible or that either the rate of the radical's initial formation or its subsequent cyclization was slow. Sugarwa and coworkers may have realized that an

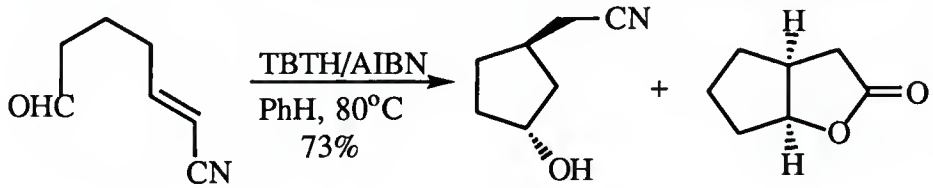
activated alkene would solve the problems.[38] They used a more electrophilic double bond of a uridine ring system in a cyclization of an aldehyde O-stannyl ketyl.



59 60

Scheme 1-17

In 1989, Enholm and Prasad demonstrated that ketones and aldehydes readily cyclized onto tethered olefinic appendages.[39] As shown in Scheme 1-18, cyclized products were produced by a 5-exo-trig cyclization of an activated olefin. A low yield of cyclization was obtained when an unactivated olefin system was used. Enholm and Burroff also obtained both



61 62 63

Scheme 1-18

spiro and fused bicyclic ring systems by tandem cyclizations with this methodology.[40] Additionally, they examined the behavior of α,β-unsaturated ketones and their cyclizations and additions to activated olefins. Highly functionalized monocyclic and bicyclic cyclopentanes were obtained.[41]

Unfortunately, there have been no studies of α,β-unsaturated ketones and aldehyde partners.[39-41] A reactivity pattern which significantly differed from these early studies

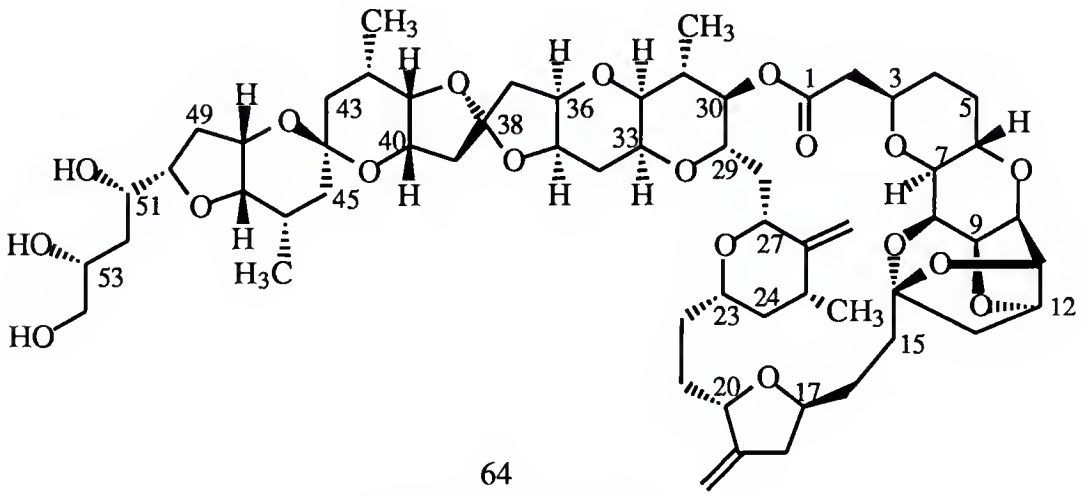
was discovered which we now believe to be the first examples of a free radical aldol-like reaction promoted by TBTH.

Chapter 3 of this dissertation discusses the intramolecular coupling of aldehydes to α,β-unsaturated ketones with tributyltin hydride and our interesting results. Since both aldehydes and ketones can form O-stannyl ketyls, more than one product can be obtained by different pathways. Deuterium-labeling and single crystal x-ray studies provided possible cyclization mechanisms.

CHAPTER 2

A SYNTHETIC APPROACH TO THE C_{44}-C_{54} PORTION OF HALICHONDRIN B USING A MOFFAT-TYPE CYCLIZATION

Halichondrin B (64) (Scheme 2-1) is an antitumor polyether macrolide isolated from *Halichondria Okadai*, a black sponge found off the Pacific coast of Japan, in early 1986 by Yoshimasa Hirata and Daisuke Uemura.[6a,b] They obtained only a very minute 12.5 mg of 64 from a huge sample of 600 kgs of sponges. Scientists from Japan and the National Cancer Institute confirmed that Halichondrin B is a currently, medicinally important antimitotic agent which shows great promise with remarkable preliminary cytotoxicity studies.[6d]



64

HALICHONDRIN B

Scheme 2-1

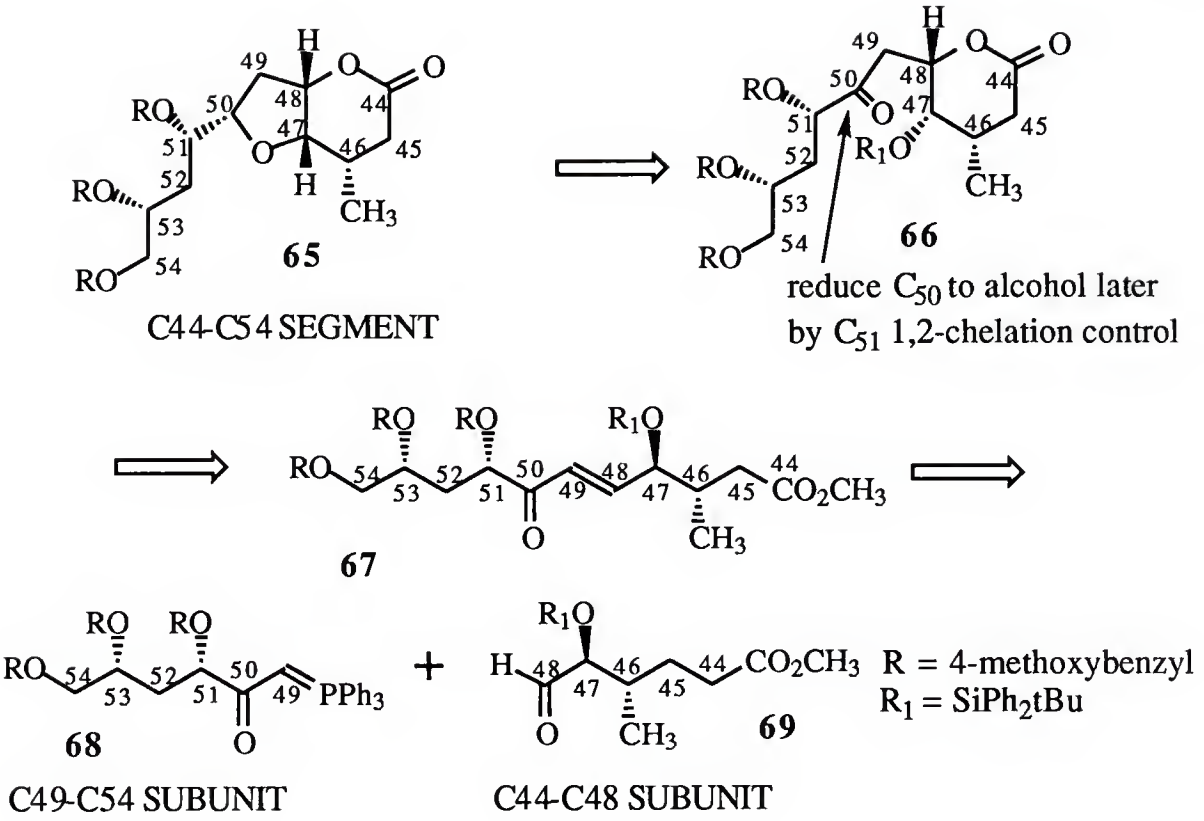
The structure of the molecule, as determined by X-ray analysis, has 1.) a long unbroken chain of carbon atoms, 2.) 32 asymmetric centers, 3.) an array of cyclic ether rings, in which two are *cis*-fused and two are tetrahydropyrans, 4.) 3 ketal linkages, of which 2 are spiro, involving a 1,6-dioxaspiro[4.4]nonane system. The absolute stereochemical structure of halichondrin B has been correlated to a single crystal x-ray of a less bioactive relative, the p-bromophenacyl ester of norhalichondrin A.[6b]

Several synthetic constructions of portions of halichondrin B by Kim and Salomon[6f] have appeared and a recent, but lengthy, total synthesis of 64 has been completed by Aicher et al.[6e] in the Spring of 1992. We have started a synthetic approach which is highly convergent and shorter than any other synthetic route. In this dissertation we will only be concerned with the far left side of 64, or the C44-C54 precursor.

Synthetic Plan of the C_{44} to C_{54} Precursor

The key features of the route to 65 are shown in Scheme 2-2, and are numerically listed below:

1. The target 65 can be antithetically disconnected to acylic fragment 67 by assuming C50 is a ketone which can be reduced later to the proper alcohol stereochemistry by well-established 1,2-chelation control, as in 66. The lactone moiety can be disconnected to reveal a Moffat-type cyclization with the C44 carboxylic acid.



Scheme 2-2

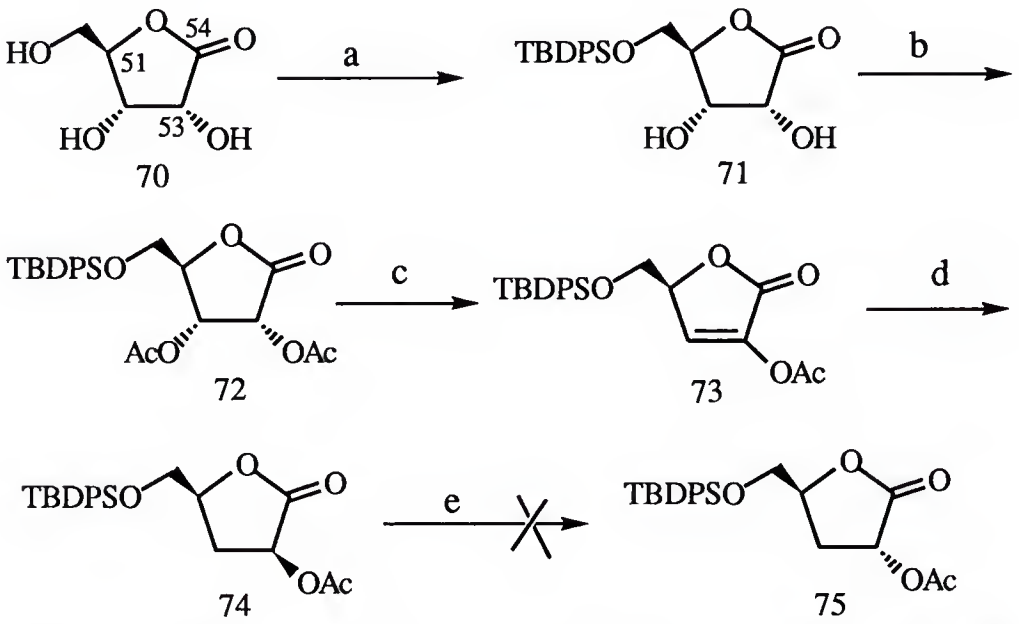
2. The C44 spiroketal in 64 is thermodynamic and it can be equilibrated with acid and water.

3. The stereochemistry of C48-C49 in 66 is equatorial and can be epimerized by a Moffatt-type equilibration.[12]

4. Disconnection of the C48-C49 double bond in 67 reveals two simple chiral nonracemic subunits, 68 (C49-C54) which can be generated by a carbohydrate template and 69 (C44-C48) which can be prepared by asymmetric epoxidation technology.

Synthesis of the C_{49}-C_{54} subunit 68

We selected well-known D-ribonolactone (70) as the starting material (1 g/$4.00, 90%, Aldrich) which has the requisite absolute stereochemistry for our route (Scheme 2-3). A highly selective protection of primary alcohol 70 with tert-butyldimethylsilyl chloride and subsequent esterification of the remaining hydroxyls afforded compound 71. After deoxygenation of 72 at C52 and hydrogenation of double bond of 73, the protected 3-deoxyribonolactone 74 was obtained. Attempted epimerization of 74 with the variety of bases failed to provide 75.

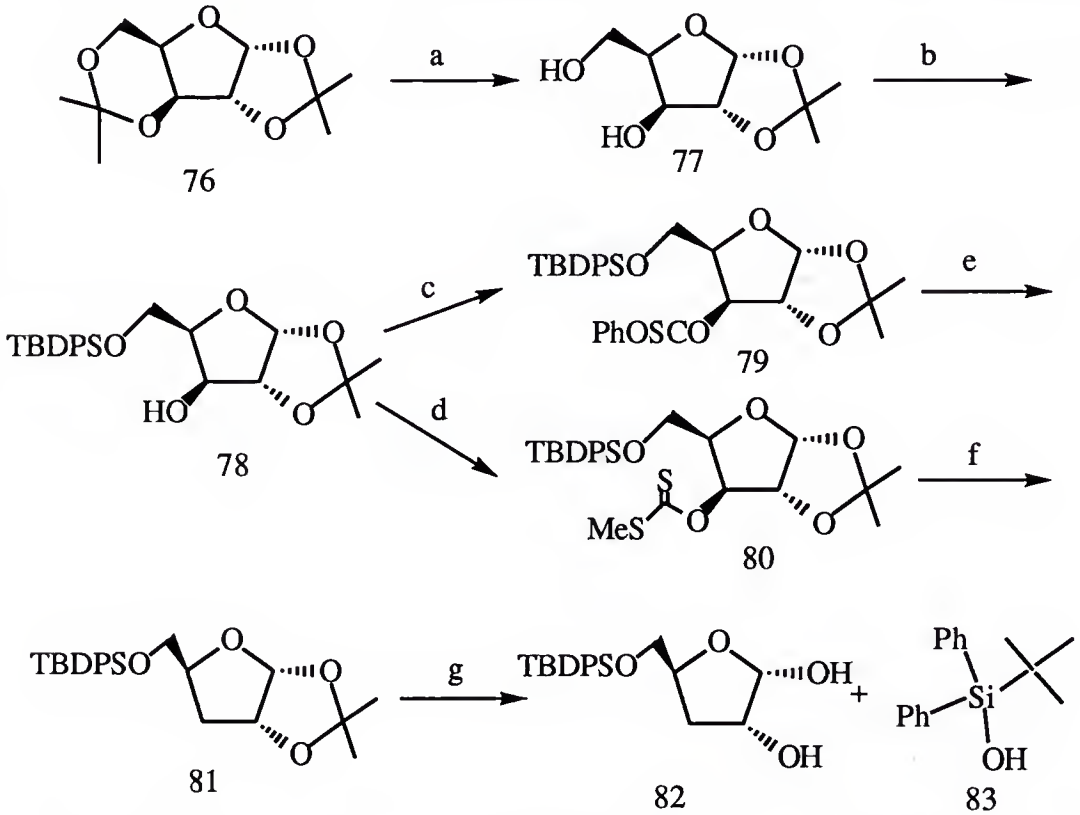


Key: (a) t-Bu(Ph)$_2$SiCl, Pyridine, 70%; (b) Ac_2O, Pyridine, O°C, 93%; (c) DBU, THF, 87%; (d) H_2, Pd/C (10%), ethanol, 94.3%; (e) DBU

Scheme 2-3

Therefore we persued a different route using 1,2:3,5-Di-O-isopropylidene-D-xylofuranose (76) (Scheme 2-4). By using this starting material, epimerization of C53 was avoided, but

oxidation of C54 to a carboxylic acid was needed later. The selective acid-catalyzed cleavage of the 3,5-isopropylidine ketal of 76, followed by silylation of the primary alcohol produced compound 78.[42,43] The key intermediate 81, with three chiral centers corresponding to C50, C53, C54 of 64, was produced by deoxygenation of 79 and 80 by two different radical reactions (methods c and d).[31,44] A similar



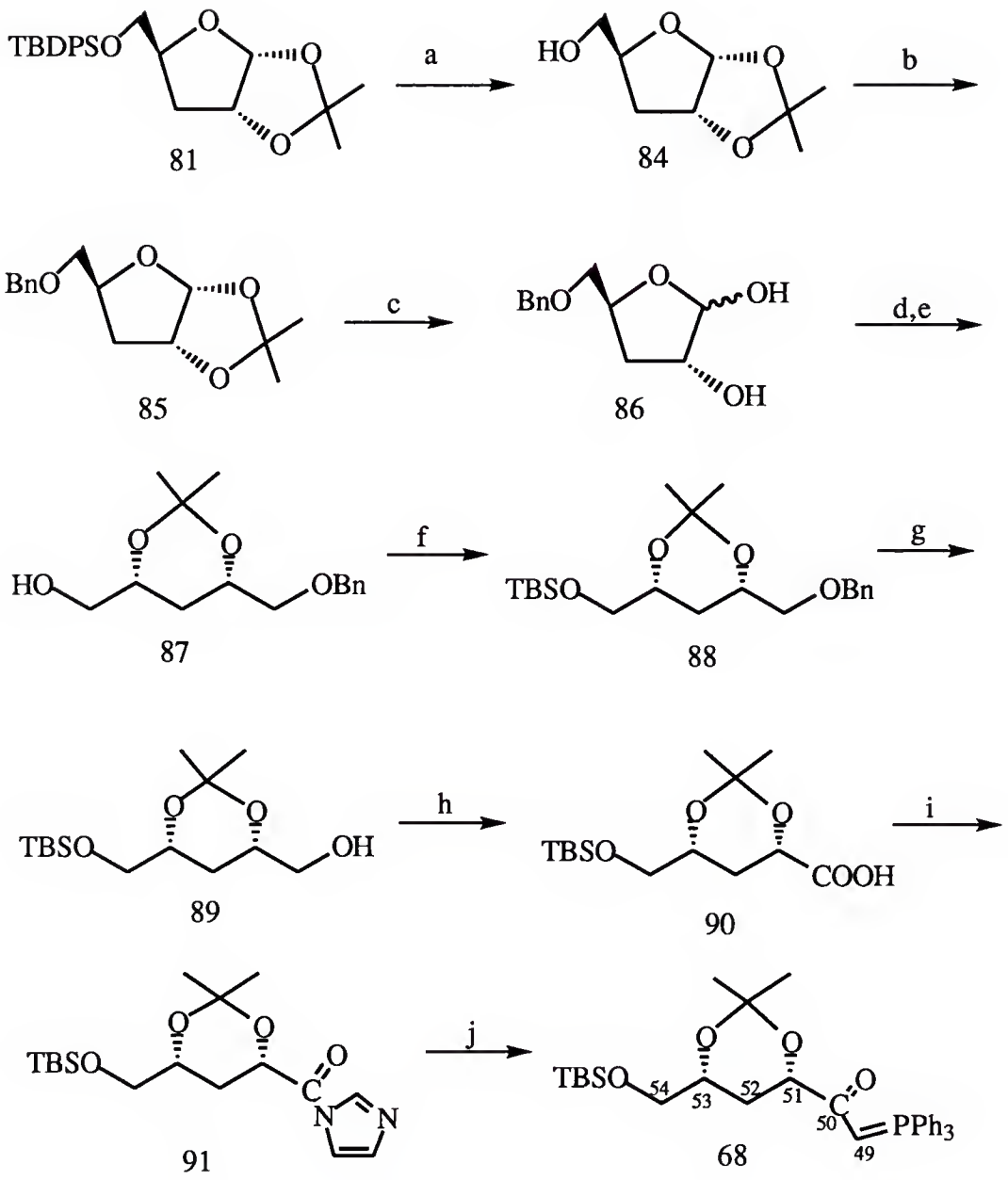
Key: (a) HOAc (70%), 80%; (b) t-Bu(Ph)$_2$SiCl, Pyridine, 92%; (c) PhOCSCl, MeLi, THF, 83.3%; (d) NaH, CS_2, MeLi, THF, 72.2%; (e) TBTH, AIBN, PhH, 80°C, 74%; (f) TBTH, Toluene, reflux, 75.3%; (g) HOAc or HCl

Scheme 2-4

mechanism for both deoxygenation reactions is shown in Scheme 1-12. Because the cost of phenyl chlorothionoformate in method c was very high, method d was used in the preparation

of 81.[44b] Because of the simultaneous cleavage of the silyl protecting group of 81 under the acidic conditions, the removal of the acetonide in 81 always gave low yield of diol 82. This is unusual because *tert*-butyldiphenylsilyl ethers have a greater stability to acids than other silyl ethers.[43]

Benzyl ethers are very stable to bases, acids and oxidative reagents. To avoid protecting group cleavage of 81, a change to the more stable C51 O-benzyl moiety of 85 proved rewarding because formation of diol 86 provided satisfactory yields (Scheme 2-5). Primary alcohol 87 was obtained by reduction of 86 and immediate protection as its acetonide. No isomers resulting from dioxolane group migration were observed.[45] Silylation with the highly active TBSTf was followed by the catalytic hydrogenation to provide alcohol 89. Jones oxidation of the primary alcohol to carboxylic acid was difficult, as both acetonide and silyl ether groups were partially cleaved in the reaction conditions. A two-step oxidation (first to aldehyde, then to carboxylic acid) also provided a low yield of product. The best result was observed using RuO_4 (produced by reaction of ruthenium (III) chloride and sodium metaperiodate) in a three solvent system. By this method, a 81% yield of carboxylic acid 90 was obtained.[46] Reaction of 90 with 1,1-carbonyldiimidazole formed imidazolide intermediate 91.[47] This intermediate can decompose in several hours at room temperature; therefore, 91 was immediately added to methylenetriphenylphosphorane to afford the stabilized Wittig reagent 68.[47b]

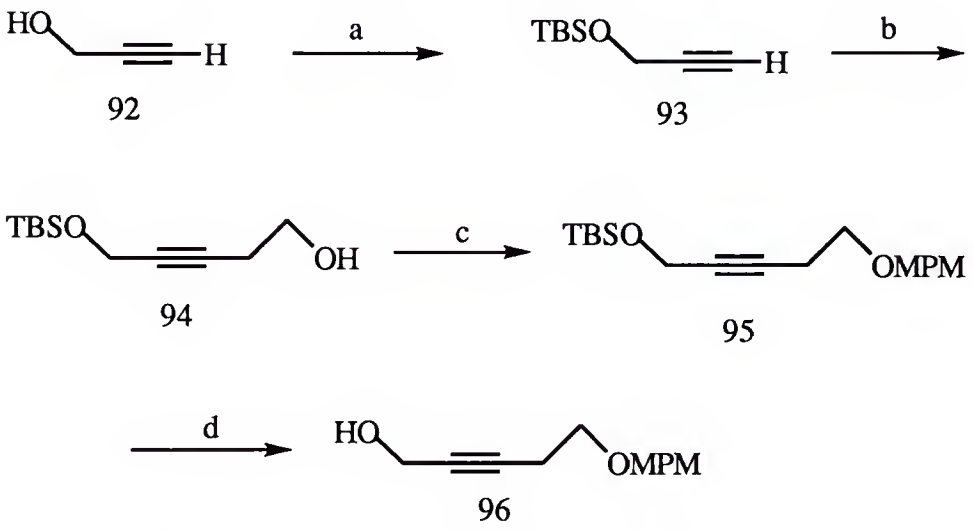


Key: (a) TBAF, THF, 83%; (b) BnCl, DMF, NaH, 89%; (c) HCl-Dioxane (1:1), 81.5%; (d) $NaBH_4$, ethanol, 85%; (e) $Me_2C(OMe)_2$, acetone, p-TsOH, 75.6%; (f) TBSTf, 2,6-lutidine, CH_2Cl_2, 100%; (g) H_2, Pd/C (10%), ethanol, 97%; (h) RuO_4, CCl_4, MeCN, H_2O, 81%; (i) 1,1-carbonyldiimidazone, THF (j) THF, CH_2=PPh_3, 52%

Scheme 2-5

Synthesis of the C_{44}-C_{48} subunit (69)

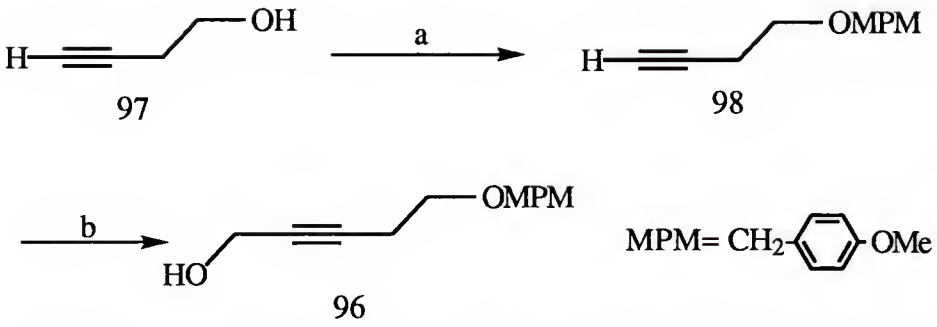
In order to convert 2-propyn-ol (92) to key intermediate 96 (Scheme 2-6), the hydroxy group of 92 was silylated, followed by the addition of a two carbon chain with ethylene oxide, which gave 94 in very low yield. Although many different reaction conditions were tried, the yield was always low.[48] Protection of the hydroxy group of 94 and selective deprotection of 95 obtained alcohol 96. Some of the TBS ether was cleaved in the presence of DMF and NaH. If THF was used instead of DMF, no reaction occurred.



Key: (a) t-$BuMe_2SiCl$, DMF, Imidazole, 81%; (b) (1) nBuLi, THF, (2) $BF_3.O(Et)_2$ then ethylene oxide, 32%; (c) MPMCl, NaH, DMF, 30%; (d) TBAF, THF, 59%

Scheme 2-6

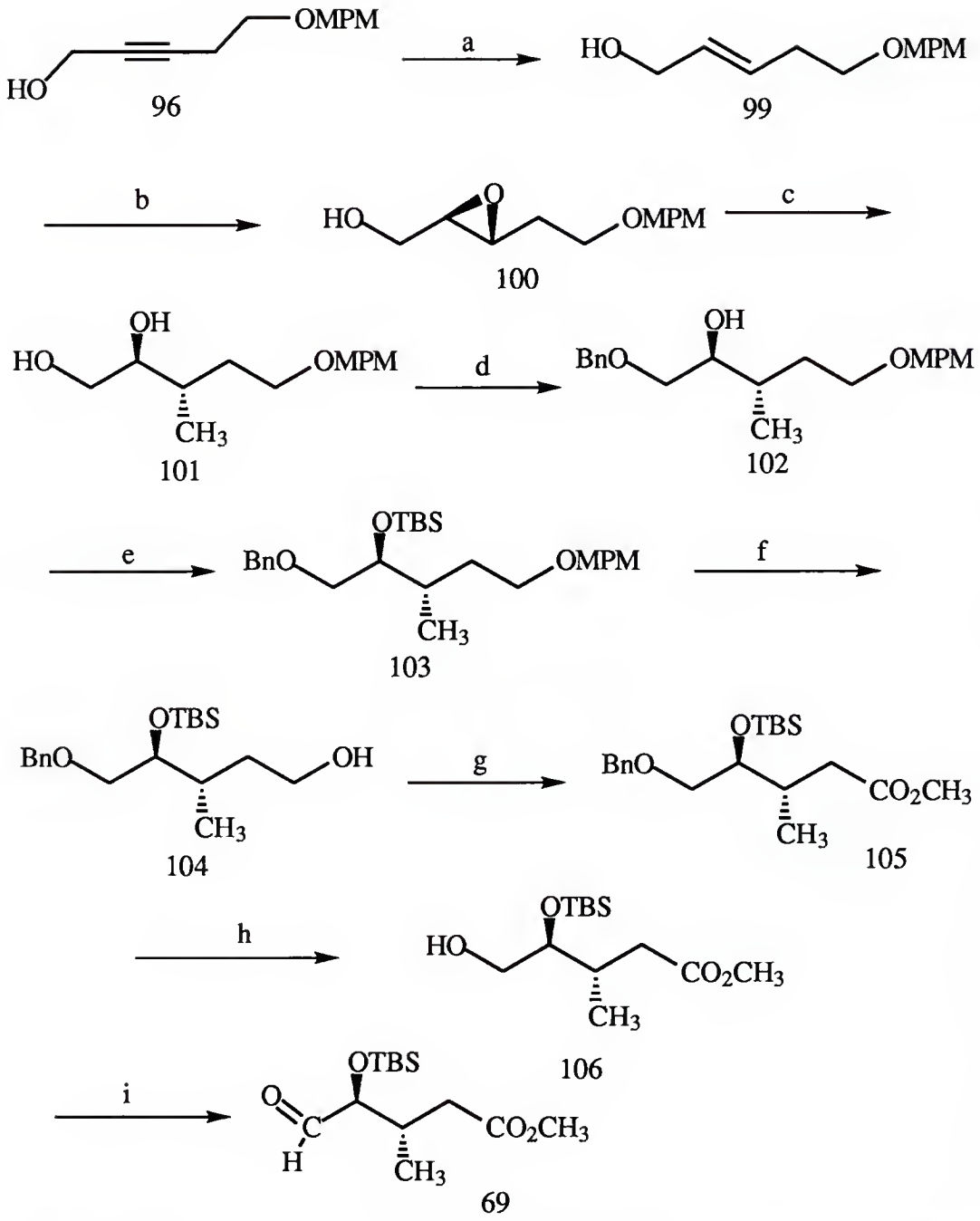
A very good alternative two-step synthesis of 96 was carried out to improve the yield (Scheme 2-7). Compound 98, readily available from 3-butyn-1-ol, was treated with para-formaldehyde to form 96 with an excellent overall yield (65%).[49]



Key: (a) MPMCl, NaH, DMF, 87.5%; (b) nBuLi, $(CH_2O)n$, THF, 73%

Scheme 2-7

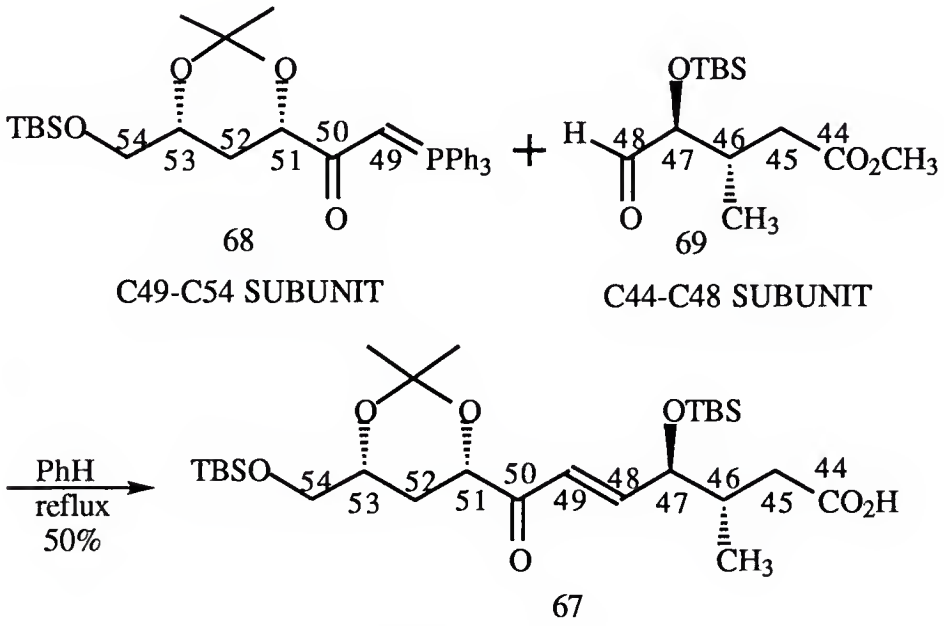
With the alcohol 96 in hand, the epoxide 100 was readily obtained from trans alkene 94 by treatment with lithium aluminum hydride and Sharpless epoxidation (Scheme 2-8).[50,51] In both of the reactions, the hydroxyl group may control the stereochemistry of these conversions. The regio- and stereoselective addition of a methyl group to epoxide 100 formed diol 101, followed by protection of the hydroxyl groups, gave 103 in good yield.[52] Although some dibenzyl ethers were formed at both hydroxyl groups in diol 105, the starting material can be recovered by catalytic hydrogenation using W-2 Raney nickel which is very selective for benzyl ether protecting groups.[53] The p-methoxybenzyl (MPM) group of compound 103 was selectively removed with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to furnish product 104.[53] Oxidation of 104 with Jones reagent and methylation with diazomethane, followed by hydrogenation afforded 106 in 75% yield.[54] Finally, treatment of 106 with Dess-Martin periodinane (DMP) reagent completed synthesis of C44-C48 subunit (69).[55]



Key: (a) LAH, ether, 85%; (b) D-(-)-DET(0.13eq), $Ti(OiPr)_4$(0.1eq), tBuOOH (2.0eq), CH_2Cl_2, sieves, -20^{0}C,87.5%; (c) Me_3Al, Hex-CH_2Cl_2, 100%; (d) BnCl NaH,DMF, 47%; (e) TBSCl, DMF, imidazole, 90%; (f) 1. DDQ, CH_2Cl_2-H_2O, (20:1), 2. $NaBH_4$, 70%; (g) (1) Jone's reagent, (2) CH_2N_2, ether, 80%; (h) H_2, Pd/C (10%), EtOH, 61%; (i) Dess-Martin, 76%

Scheme 2-8

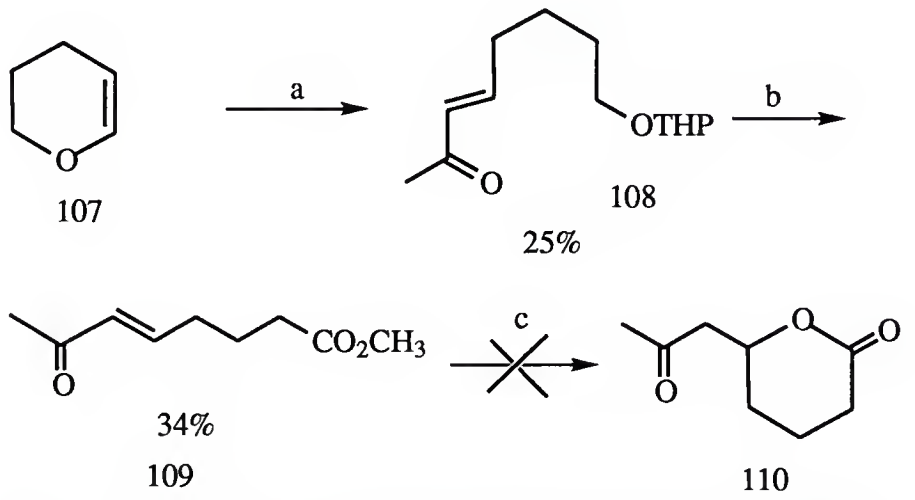
With the C44-C48 and C49-C54 subunits (69 and 68) in place, a coupling reaction was carried out in refluxing benzene to provide alkene 67 (Scheme 2-9).[56] This reaction has only been attempted one time in 32% yield. The ^1H NMR indicated sole trans alkene geometry in 67.



Scheme 2-9

Because there was only 50 mg of cyclization precursor 67 a model reaction was carried out to test the feasibility of a Moffatt-type cyclization (Scheme 1-4) in this system. Catalytic hydrolysis of 3,4-dihydro-2H-pyran 107 was followed by reaction with a methyl ketone ylide to produce the acyclic compound 108. Ester 109 was prepared by Jones oxidation and esterification of diazomethane. Lactone 110 was not observed when ester 109 was subjected to a saponifying base (LiOH) treatment. Only tar-like compounds were obtained.

Iodolactonization and reductive removal of the iodine (Process 3 of Scheme 1-2) may provide the lactone 110 because Kishi's synthesis obtained a similar intermediate using this strategy.[6]



Key: (a) 1) H_2O, HCl, 2) $Ph_3P{=}CHCOCH_3$, CH_2Cl_2; (b) 1) Jones reagent, 2) CH_2N_2, ether; (c) LiOH

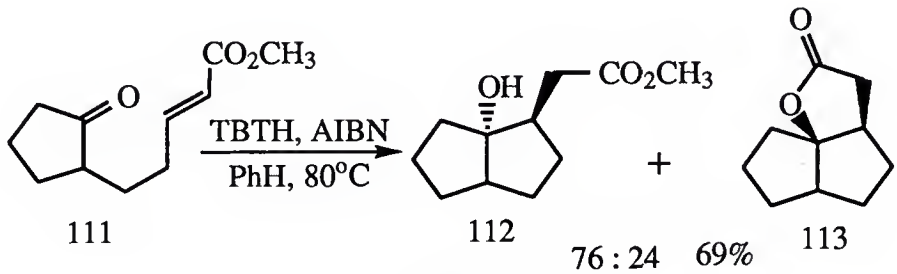
Scheme 2-10

Now we have prepared both C44-C48 and C49-C54 subunits and completed the coupling reaction to prepare key intermediate 67. Although model Moffat-type cyclizations were not successful, many other key reactions are interesting. The synthesis features useful adaptations of Sharpless asymmetric epoxidation, free radical deoxygenation of a carbohydrate ring and formation of a stablized ylide by an acyl imidazolide.

CHAPTER 3

FREE RADICAL CYCLIZATIONS OF ALDEHYDES AND α,β-UNSATURATED KETONES PROMOTED BY O-STANNYL KETYLS

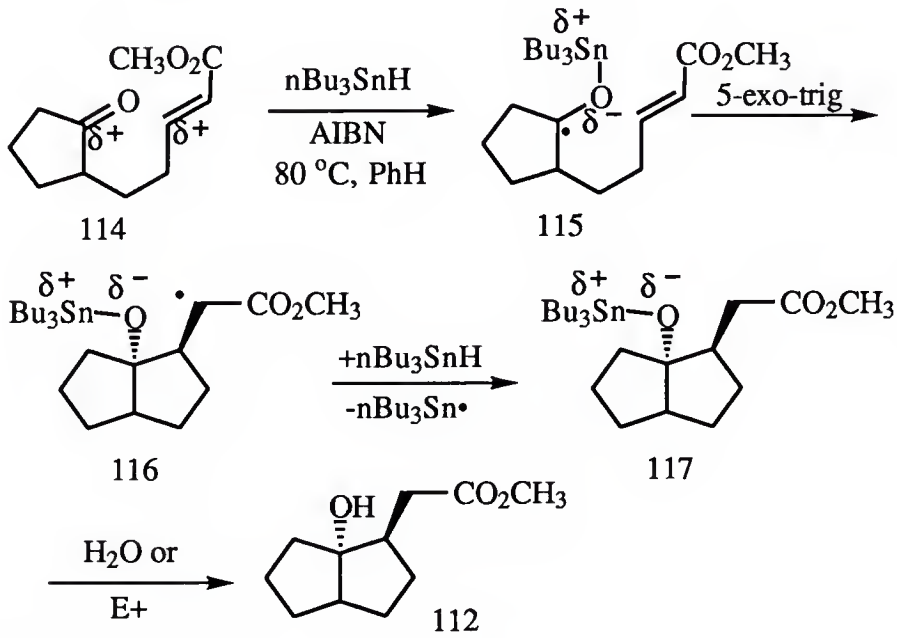
An activated olefin, as it is referred to by free radical chemists, is an alkene which possesses some type of electron withdrawing substituent such as an ester, nitrile, or aromatic ring, which functions to facilitate addition reactions to the π-system (Figure 3-1). Not only can an aldehyde readily cyclize on an activated olefin by an O-stannyl ketyl intermediate (Scheme 1-15), but a ketone also can undergo a similar reaction, as shown in Scheme 3-1.[39,57]



Scheme 3-1

The reaction is probably mediated by a homolytic chain mechanism and proceeds by the addition of a tributyltin radical to the ketone carbonyl in 114 to produce O-stannyl ketyl intermediate 115 (Scheme 3-2). Trialkyltin radical addition to a carbonyl to produce O-stannyl ketyl intermediates in simple carbonyl reductions to alcohols has

been reported.[29a] A subsequent 5-hexenyl-1-oxy cyclization, by addition to the activated olefin, produces the carbon-centered free radical intermediate 116. A transfer of hydrogen atom from tributyltin hydride then renders 117 and



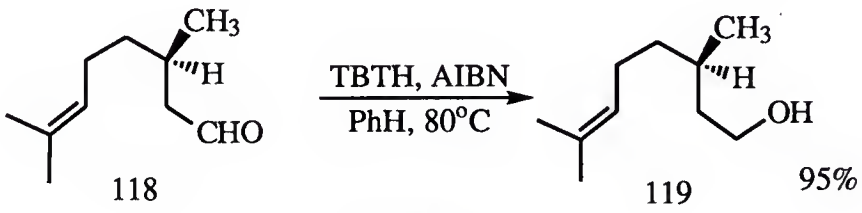
Scheme 3-2

tributyltin radical which repeats the process. It is noteworthy that prior to H_2O workup, intermediate 117 contains a useful tin alkoxide functionality and has the capability to afford other useful addends.[29a]

It has been documented that an activated alkene could also be reduced though a related process.[58-59] When tributyltin hydride reacts with an unsaturated ester or nitrile functional group, the olefin is hydrostannylated in preference to O-stannyl ketyl formation and results in a Michael-type product bearing a tributyltin moiety β- to the electron-withdrawing group.[29a] Interestingly, these adducts

were not observed as products in any of the examples attempted. We reasoned that the tributyltin radical was undergoing rapid and reversible addition to the alkene concurrently with a slower yet reversible addition to the carbonyl to form the O-stannyl ketyl, however, once the cyclization occurs, it is not readily reversible, similar to many free radical reactions. Although the syn-products were not the favored stereochemistry in the reactions, they still formed in substantial amounts (Schemes 1-18, 3-1) which helps support the idea that the cyclization is not readily reversible.

If a nonactivated olefin, citronellal (118), was treated under the same conditions as the reactions above, simple acylic citronellol (119) was produced in 95% yield. It is

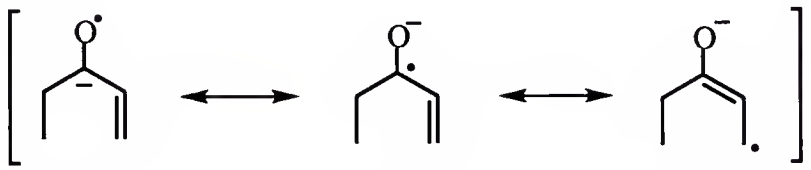


Scheme 3-3

clear from this example that the stannyl ketyl radical did not immediately cyclize and was subsequently reduced by another molecule of TBTH because the rate of cyclization is slow with nonactivated olefins and competes with the rate of hydrogen atom abstraction from TBTH. This result showed that an activated alkene was a critical element for cyclization. The frontier molecular orbital theory, as presented in Chapter 1, may explain why the activated alkene was important

to this kind of reaction. With ketyls, the tin alkoxylate of 55 imparts some negative character onto the radical, thus making the radical even more nucleophilic than a simple carbon-centered radical by increasing the energy of the SOMO. An electron withdrawing substituent on the olefin reduces the LUMO energy to such an extent that it has better orbital overlap with the higher energy SOMO's of ketyl (Figure 1-1).[24]

Enholm and Kinter examined the behavior of α,β-unsaturated ketones and their intramolecular additions to activated olefins.[41] Resonance contributors, supported by Huckel calculations, indicate the radical anion of an α,β-unsaturated



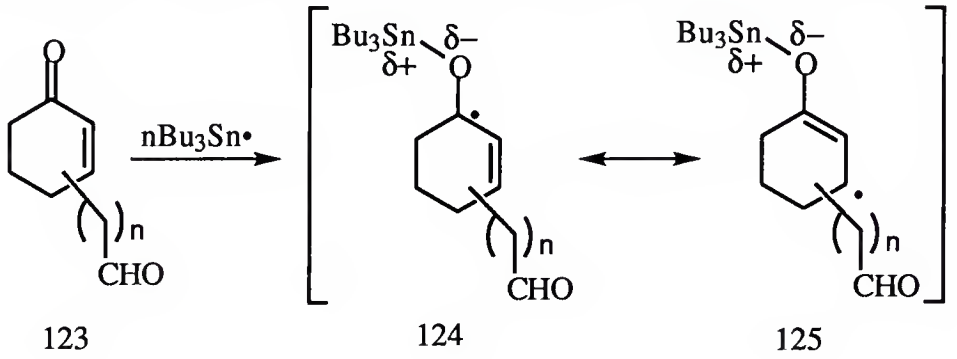
120 121 122

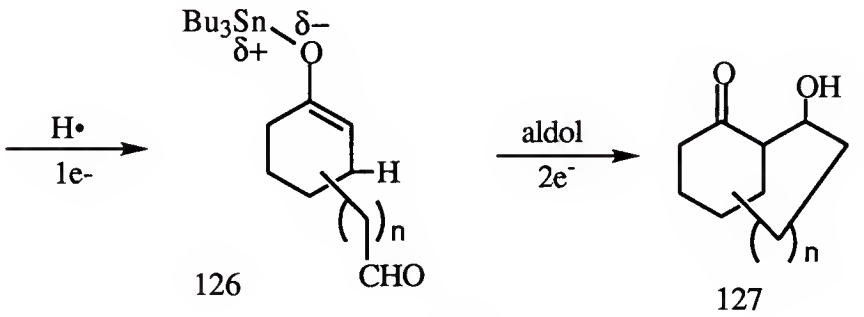
Scheme 3-4

ketone (Scheme 3-4) has 50% of the radical density located on the β-carbon 122, while the remaining portion is divided equally between the carbonyl carbon 121 and the carbonyl oxygen 120.[60] In each case, the free radical on the electron-rich β-carbon (instead of the actual tin ketyl radical) cyclized onto an electron-deficient olefin.

Precursors used to form O-stannyl ketyls generally have only one aldehyde or ketone to react with $nBu_3Sn\bullet$. This chapter will examine compeditive behavior of α,β-unsaturated ketones and aldehyde partners with tributyltin radical

($nBu_3Sn\bullet$) which has never been studied before. Compound 123 bears a choice of two potentially reactive carbonyls. Previous studies and steric arguments might favor attack at the aldehyde leading to O-stannyl ketyl addition to the



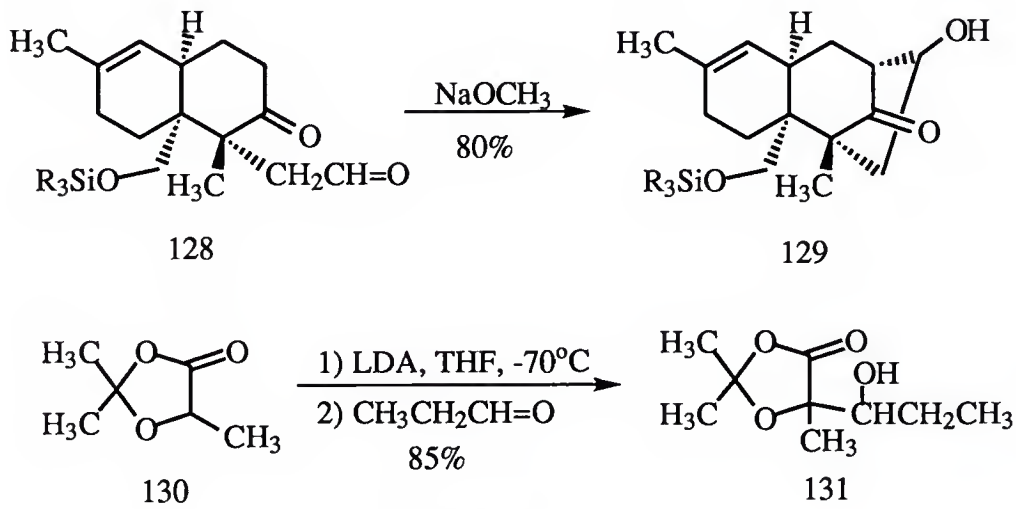


Scheme 3-5

β-olefin site or direct reduction to an alcohol.[39] Alternatively, $nBu_3Sn\bullet$ attack at the cyclohexenone moiety in 123 affords resonance stabilized allylic O-stannyl ketyl 124 ↔ 125. If hydrogen atom transfer occurs regioselectively at the β-position of 125, a tin enolate 126 would be prepared by a novel approach. The resulting enolate can now undergo an intramolecular aldol with the tethered aldehyde to prepare the bicylic structure 127 (Scheme 3-5). It is also possible that the aldol reaction could occur before the hydrogen atom transfer. Either pathway would produce the same product. The

interesting combination of free radical and enolate chemistry required in this reaction exemplifies a new rapidly-emerging class of sequential one- and two-electron reactions.[61]

This chapter describes preliminary results for this new cyclization protocol where the annulation is the result of a directed tin aldol based on a 2-electron mode of reactivity. These studies also introduce a mild alternative to current enolate chemistry which avoids NaH, LDA, LHMDS, or other strongly reductive conditions such as dissolving metal media (Scheme 3-6).[62] To test this hypothesis, cyclohexenones

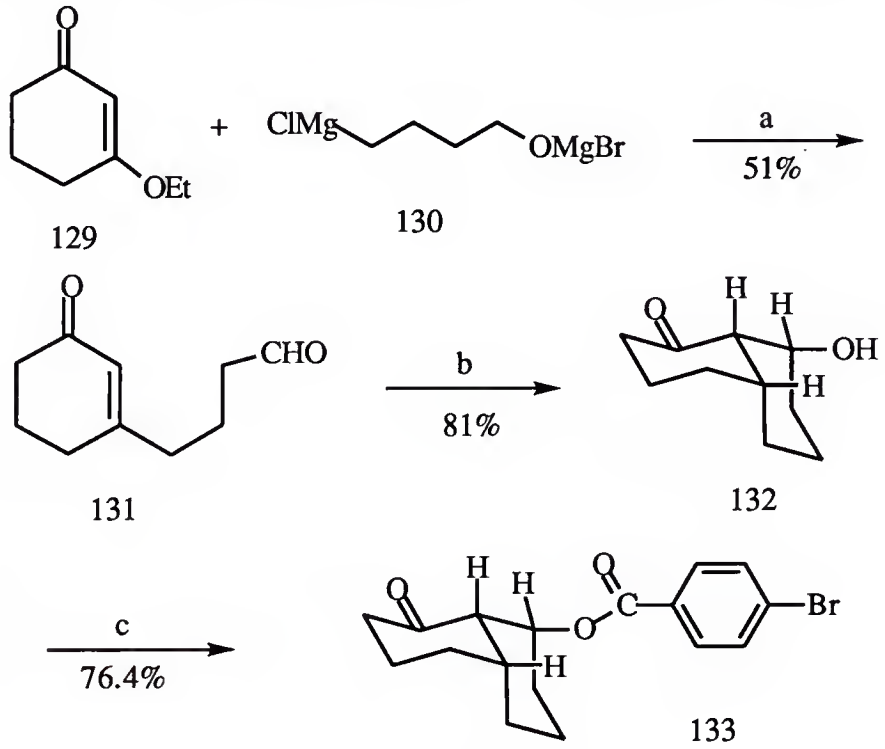


Scheme 3-6

similar to 123 were constructed bearing suitably tethered aldehydes as electrophiles and their tin enolate cyclizations were then examined. To the best of our knowledge, neutral free radical approaches to aldol chemistry using nBu_3SnH have not been examined.

Aldol precursor 131 (Scheme 3-7), bearing an aldehyde tether in the C_3-position on a cyclohexanone ring, was

readily prepared from Grignard reagent 130 derived from 4-chlorobutanol in a reaction with 3-ethoxy-2-cyclohexanone (129), followed by a standard Swern oxidation.[63,64] The tin enolate cyclization was promoted by treatment of 131 with



mp 120.8-121.7

(a) 1. THF-PhH; 2. Swern oxidation; (b) nBuSnH, AIBN, PhH, 80°C

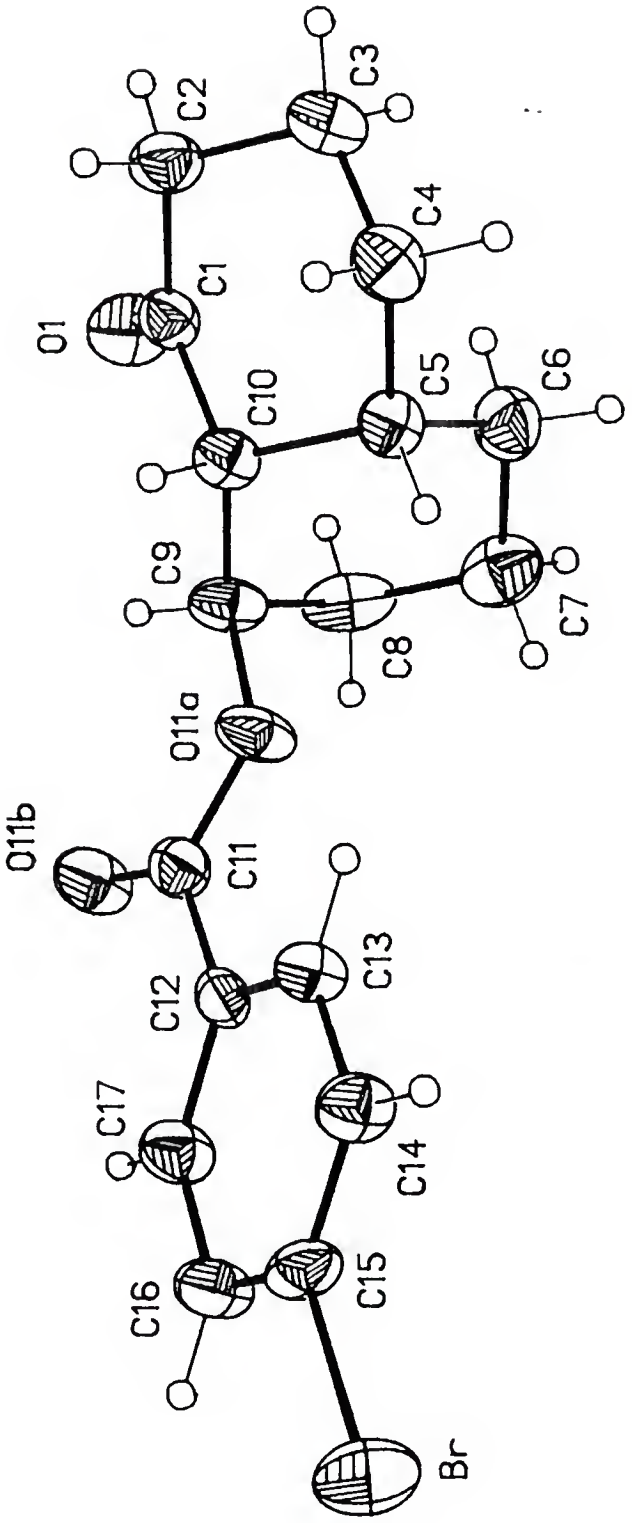
(c) $ClCOC_6H_4Br$, THF-Pyridine

Scheme 3-7

tributyltin hydride under free radical conditions which afforded the cis-decalone alcohol 132 in 81% yield. Interestingly, three new stereocenters resulted from the cyclization, one bearing the alcohol and two arising from the cis-decalin ring fusion. Only a single product could be isolated (>50 : 1) and other diastereomers could not be detected by NMR or chromatographic methods. To unambiguously insure the structure and stereochemistry were correct, a

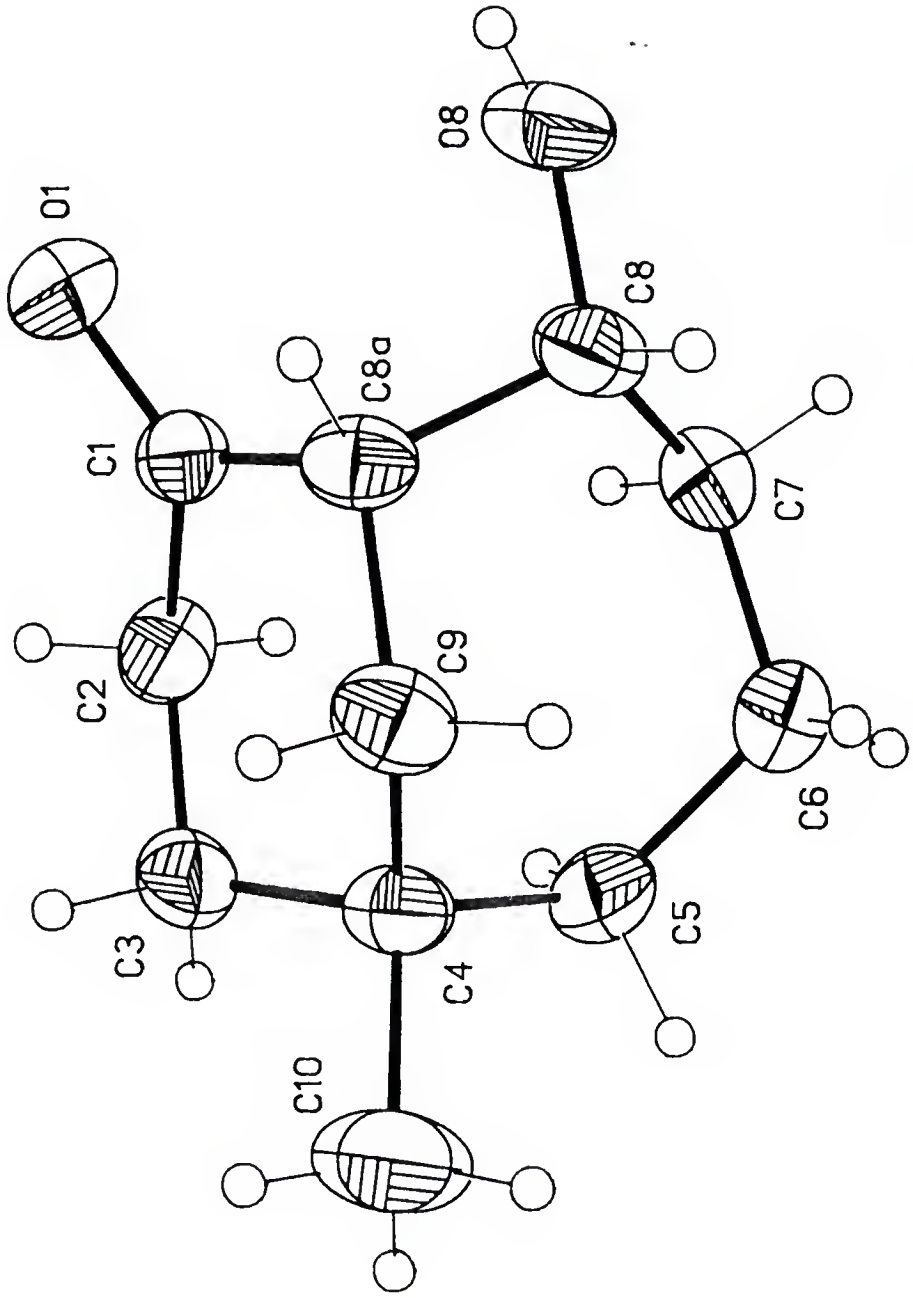
single crystal x-ray crystallography needed to be obtained. Compound 132 had to be converted into its *p*-bromobenzoate ester (133) prior to stereochemical confirmation by x-ray studies.[65] This gave not only better quality crystals, but incorporated a heavy atom (Br) into the structure. An O.R.T.E.P. plot of 133 is shown in Figure 3-1. Spirocyclization of the β-carbon-centered radical of 131 with the tethered aldehyde may have been particularly blocked due to the formation of a hindered quaternary center, thus, a second example where this was not possible was examined next.

Aldehyde 138 (Scheme 3-8) bears a different pattern of substitution on the cyclohexenone and was constructed by adapting the general protocol of Becker et al..[66] It was prepared from the Robinson annulated product 134 which was protected with concomitant olefin migration to afford 135.[66,67] Introduction of a 4-carbon alcohol appendage by ozonolysis, reduction, and deprotection gave ketone 137.[66] Aldehyde 138, the O-stannyl enolate precursor, was prepared by Swern oxidation.[64] We were pleased in this case to find the tin hydride-mediated cyclization gave a seven-membered annulated ring, constructing bicylic alcohol 139 as a crystal in 62% yield. As with the example above, no other diastereomers were present by GC, TLC or NMR, however, some unreacted 138 remained (ca. 17%) in this case. Single crystal x-ray studies confirmed the stereochemistry of 139, in which the sterically congested hydroxyl was endo in the bicy-



X-ray Structure of 133

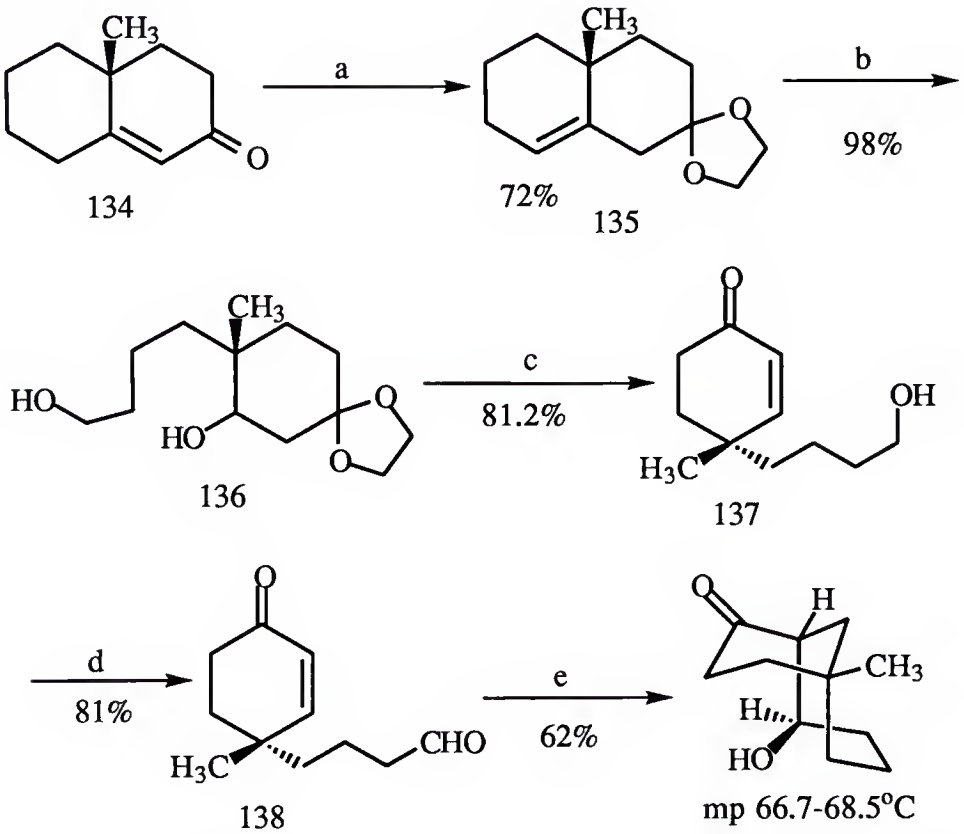
Figure 3-1



X-ray Structure of 139

Figure 3-2

clo[4.3.1]nonane skeleton. An O.R.T.E.P. plot of 139 is shown in Figure 3-2.

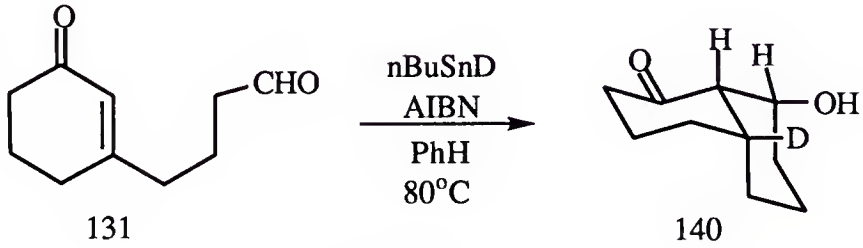


Key: (a) $(HOCH_2)_2$, pTsOH, PhH, Heat; (b) 1. O_3; 2. $NaBH_4$; (c) THF-H_2O, $(HO_2C)_2$, heat; (d) Swern ox.; (e) TBTH, AIBN, PhH, 80°C

Scheme 3-8

Two chemical studies, shown in Schemes 3-9 and 3-10, were conducted which support the aldol cyclization by the allylic O-stannyl ketyl mechanism (Scheme 3-5). Compound 131 was reacted with tributyltin deuteride and formed only deuterated compound 140 after stopping the reaction at ca. 30% completion, as shown in Scheme 3-9. This confirmed the regiochemically favored location of radical at the ring

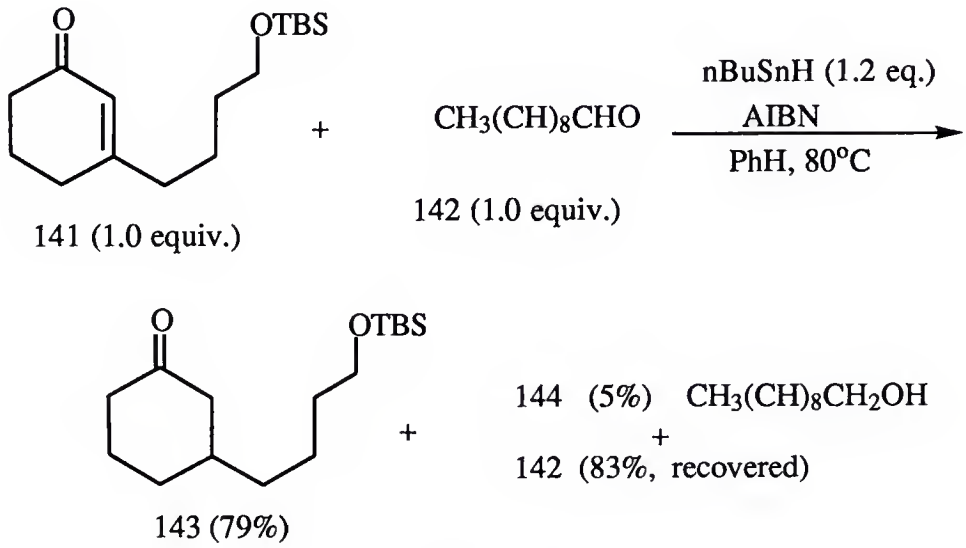
juncture in the annulation reaction; however, it does not rule out the O-stannyl ketyl formation at the aldehyde.



131 140

Scheme 3-9

Thus, an alternative explanation for the cyclization is that the tin ketyl forms at the aldehyde carbonyl site and cyclization occurs by attack at the α-position of the enone. This possibility cannot be ruled out, but seems unlikely, because an O-stannyl ketyl is a nucleophilic radical and intramolecular attack at the electrophilic β-position of the alkene should be favored.[39,41] Had this occurred in the case



141 (1.0 equiv.)

142 (1.0 equiv.)

143 (79%)

Scheme 3-10

of 138, a six-, rather than the observed seven-membered ring would have prevailed.

A study to distinguish between the ketyls of the aldehyde and the 2-cyclohexenone compared 141 and decanal (142) in a simple competition experiment, shown in Scheme 3-10. As predicted, 143 was formed more rapidly than 144, which suggests a preference for the resonance stabilized allylic O-stannyl ketyl of the 2-cyclohexenone over the O-stannyl ketyl of the aldehyde. The small amount of decyl alcohol (144) formed due to the dilution of the reaction mixture or from the slight excess (1.2 equiv.) of tin hydride used.* On the basis of these observations, we propose that free radicals are not involved in the cyclization step, but rather it proceeds via the tin enolate (Scheme 3-5).

To summarize these findings, a new free radical method for the construction of carbon-carbon bonds from allylic O-stannyl ketyls has been developed. A directed aldol-type carbonyl addition promoted by nBu_3SnH led to annulated cycloalkanols, where up to three new stereocenters resulted in a highly stereoselective manner. These studies provide a neutral method to prepare tin enolates which may have future applications to intermolecular aldol-type reactions.*

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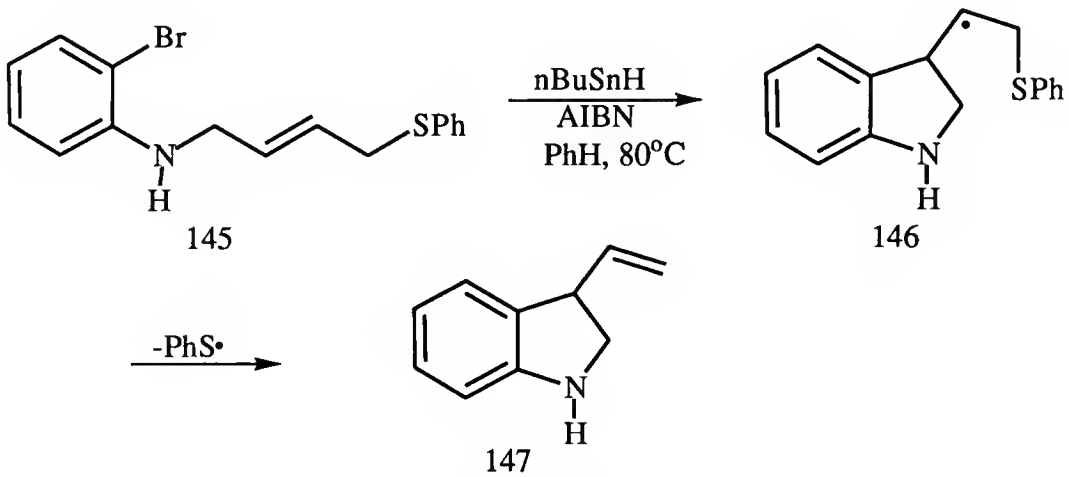
* Earlier studies have shown that either moiety can be reduced with tin hydride.[29a] Low concentrations were employed to separate reactive partners and prevent a bimolecular aldol. This allowed the tin enolate to remain unreacted until workup.

CHAPTER 4

CYCLIZATION AND S_N' FRAGMENTATION REACTIONS PROMOTED BY O-STANNYL KETYLS

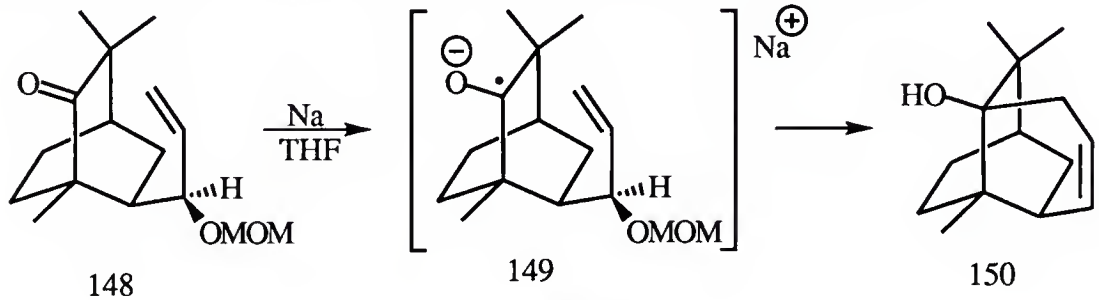
In Chapter 1, Schemes 1-7 and 1-8 demonstrate the intramolecular anionic S_N' elimination reaction. A similar process can be found in the radical domain.[23,26] Compared to the anionic reactions, fewer studies of the radical process exist, which is sometimes called β-scission or "fragmentation" and can occur after cyclization.[29e] Interesting work in this area has been produced in the laboratories of Curran, Keck, Danishefsky and others.[68] A specific example from Ueno's group is shown in Scheme 4-1.[69] Functions which are ejected here include, $R_3Sn\bullet$, PhS•, and Cl•.



145 146 147

Scheme 4-1

Although tin ketyls have been used to perform a variety of synthetic tasks, surprisingly, they have never been examined in intramolecular cyclizations followed by S_N' elimination reactions. A single study describes two bimolecular examples with SmI_2.[70] In a series of closely related reactions, bicyclic ketones with general structure 148 were used to construct several natural products by using sodium ketyls (Scheme 4-2), all with patchouli alcohol skeleton 150.[71] No other studies in this area exist.



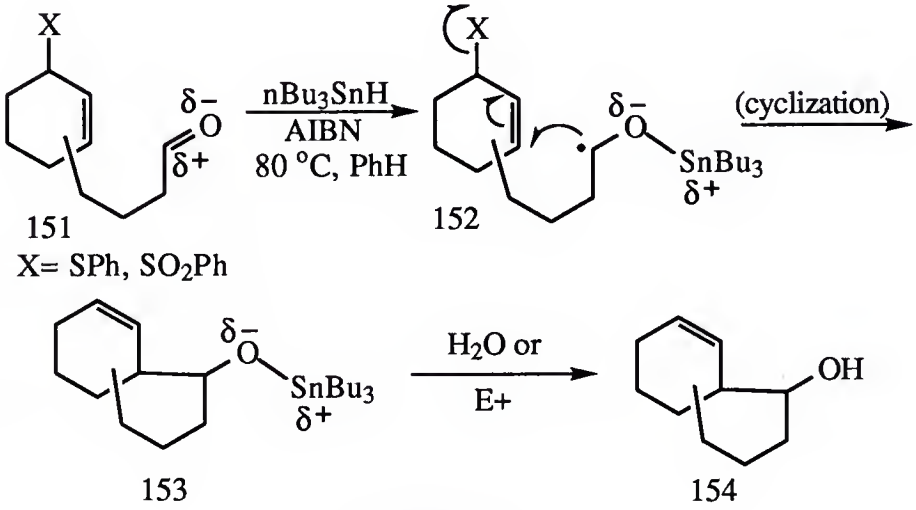
148 149 150

Scheme 4-2

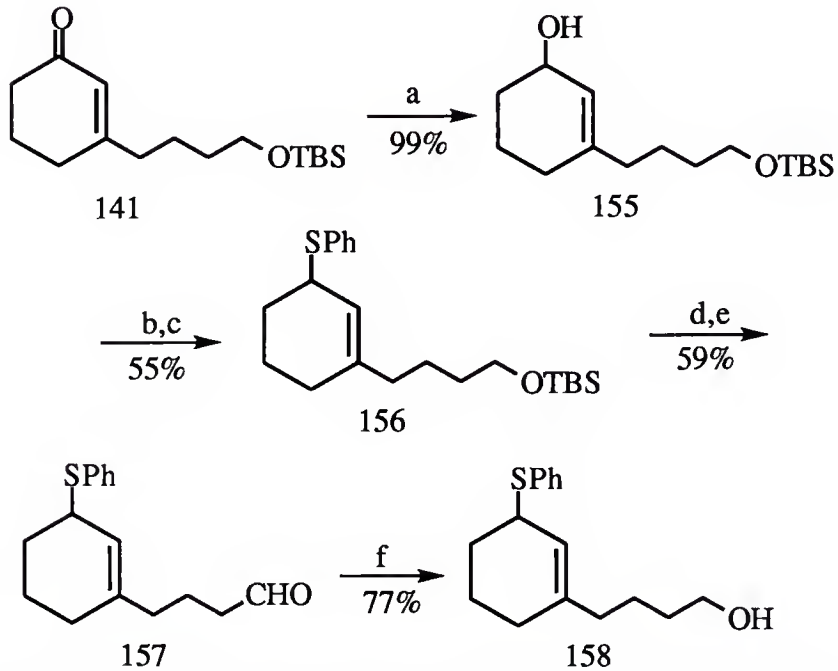
The proposed plan for a tin ketyl S_N' cyclization is presented in Scheme 4-3. Tributyltin radical addition to the aldehyde carbonyl of the starting material generates the O-stannyl ketyl 152. This ketyl radical subsequently cyclized with the olefin by a 5- or 6-exo-trig processes. The radical elimination of leaving groups (•SPh and $•SO_2Ph$) should give the tin alkoxide 153, which could then be quenched by water to yield the final cyclized compound 154.

We took advantage of previous work (see Chapter 3) and used 141 as a starting compound which was first reduced to alcohol 155 with high yield. With the sterically hindered system of 155, simple displacement of the activated hydroxyl

group by benzenesulfinate anion gave a very low yield (<10%) of 156. It was later discovered that the methanesulfonate



Scheme 4-3

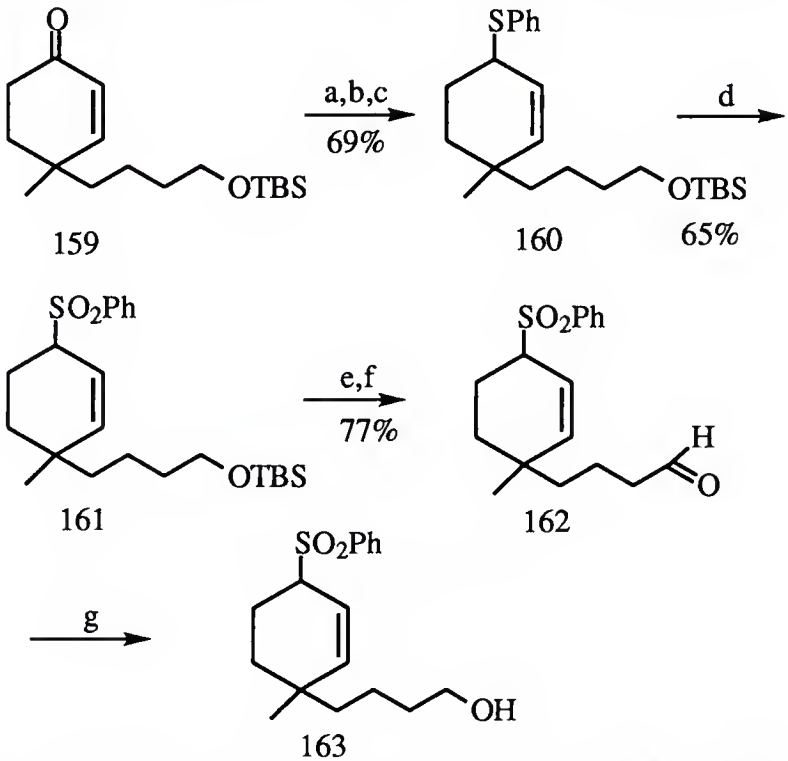


Key: (a) $NaBH_4$, CH_3OH (b) NEt_3, CH_3SO_2Cl, CH_2Cl_2 (c) nBuLi, PhSH, THF; (d) TBAF, THF; (e) Swern ox.; (f) TBTH, AIBN, PhH

Scheme 4-4

generated in situ was easily displaced by phenylsulfide anion.[72] Deprotection and Swern oxidation of 156 furnished key intermediate 157, which was then subjected to radical reaction conditions. Unfortunatly, the starting aldehyde was just reduced to primary alchhol 158 (Scheme 4-4). We thought that there were two possible resons for this failure: 1) spiro-cyclization at the β-carbon of 157 was too hindered; 2) phenyl sulfide was not a very good leaving group; thus, a second example was examined next (Scheme 4-5).

Aldehyde 162 bears a different pattern of substitution on the ring which has an allylic sulfone group and does not lead



Key: (a) $NaBH_4$, CH_3OH (b) NEt_3, CH_3SO_2Cl, CH_2Cl_2 (c) nBuLi, PhSH, THF; (d) m-CPBA, pyridine; (e) TBAF, THF; (f) Swern ox.; (g) TBTH, AIBN, PhH

Scheme 4-5

to the formation of a hindered quaternary center between the β-carbon and the tethered aldehyde. Compound 162 was obtained by a synthesis analogous to Scheme 3-4 except oxidation of sulfide 160 produced the sulfone 161. Radical reaction of aldehyde 162 still produced the primary alcohol 163.

Both examples show that with these functionalities, a tin ketyl abstracts a hydrogen atom faster than it adds to a double bond. We conclude from these studies that this general approach to S_N' cyclizations will not be successful and thus, this work was halted at this point. Futher studies may involve the use of trialkyltin functions which are S_N'-eliminated and the use of acyclic precursors.

CHAPTER 5
EXPERIMENTAL SECTION

General

NMR spectra were recorded on a QE-300, or VXR-300 MHz instrument. Residual chloroform (δ 7.24 ppm) was used as the internal reference for spectra measured in $CDCl_3$. IR spectra were recorded on a Perkin Elmer 1600 infrared spectrophotometer. Melting points were acquired on a Thomas Hoover capillary melting point apparatus and were uncorrected. All reactions were conducted in oven-dried (120°C) glassware under atmospheres of dry argon. Air- and moisture-sensitive compounds were introduced via syringe. Combustion analyses were performed by Chemistry Department, University of Florida, or Atlantic Microlabs, Inc. (Norcross, GA).Mass spectra and exact mass measurements were performed on Finnigan MAT95Q, Finnigan 4515, or Finnigan ITD mass spectrometers. All GC experiments were performed on a Varian 3500 capillary gas chromatograph using a J & W fused silica capillary column (DB5-30W; film thickness 0.25 μ).

All reagents and solvents were analytical grade and were used as received. Tetrahydrofuran (THF), toluene, benzene were distilled from sodium metal benzophenone ketyl. Analytic TLC was performed with precoated silica gel plates (0.25 MM)

using phosphomolybdic acid in ethanol followed by heating as an indicator. Flash chromatography was performed using (230-400 mesh) silica gel by standard flash chromatographic techniques.

Experimental Procedures and Results

Compounds **71→74**

These identical to that prepared by Barret and coworkers.[6g]

1,2-Isopropylidene-5-O-Diphenyl-t-butylsilyl-β-xylofuranose(**78**).[42,43]

The diisopropylidenexylofuranose (**76**) (57.22 g, 0.249 mol) was dissolved in 70% acetic acid (150 ml), and the mixture was stired for 24 h at room temperature, and finally evaporated. The residue was evaporated with toluene (4 x 150 ml) and added brine (50 ml). The aqueous phase was extracted with ethyl acetate (3 x 150 ml) and the combined extracts were dried and evaporated under reduced pressure to yield 1,2-O-Isopropylidene-D-xylofuranose (**77**) (37.9g, 80%). The proton and ^{13}C spectra were identical with that of authenic sample[42]; 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.31 (1H, s), 1.48 (1H, s), 3.48 (2H, m), 4.18 (1H, m), 4.42 (1H, d), 4.6 (1H, s), 5.10 (1H, s), 5.59 (1H, d); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 25.95, 26.49, 60.31, 75.78, 79.28, 85.23, 104.54, 104.56, 111.60.

Diol **77** (15g, 78.8 mmol), imidazole (12.3g, 181 mmol), and tert-butyldimethylsilyl chloride (23.84g, 86.7 mmol) were stirred in DMF (25 ml) at room temperature for 12 h. The reaction mixture was partitioned between diethyl ether (150 ml) and water (150 ml) and the aqueous phase extracted with diethyl ether (3 x 100 ml). The organic phase was washed with water, dried over MgSO4, and concentrated in vacuo to afford, after recrystallization from hexane, alcohol **78** (30.7g, 91%) as a white crystalline solid, m.p. 69-71°C. Rf=0.49 (35% THF-hexanes) 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.05 (9H, s), 1.32 (3H, s), 1.46 (1H, s), 4.09-4,17 (4H, m), 4.36 (1H, s), 4.53 (1H, d), 5.99 (1H, d), 7.35-7.50 and 7.66-7.73 (10H, m); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 18.97, 26.08, 26.60, 26.69, 62.61, 76.59, 78.41, 85.31, 104.86, 111.37, 127.79, 127.81, 129.93, 135.39, 135.58; IR (KBr, film) 3470 (s), 2930, 2855, 1428, 1388, 1219, 1116 (s), 1011 (m), 821, 708; Anal. Calcd for $C_{24}H_{32}O_5Si$: C, 67.26; H, 7.53. Found: C, 67.35; H, 7.56.

1,2-Isopropylidene-3-O-phenyl-chlorothionoformate-5-O-Diphenyl-t-butylsilyl-b-xylofuranose (**79**).[31]

To a stirred solution of 0.23g (0.54 mmol) of alcohol **78** in 6 ml of THF was added 0.393 ml (1.5 M in ether) of methylithium in an ice bath and stirred vigorously. After 0.5 h, phenyl chlorothionoformate (82 ml, 57 mmol) was added and the reaction mixture was warmed up to room temperature for one h. After the usual work-up, chromatography on silica (eluant diethyl ether-hexane; 20:80) afforded compound **79** as

a yellow, thick oil (0.246g, 83.3%). Rf=0.61 (35% THF-hexanes)300 MHz ^{1}H NMR ($CDCl_3$) δ 1.07 (9H, s), 1.33 (3H, s), 1.55 (1H, s), 3.97 (2H, d, J=23 Hz), 4.58 (1H, m), 4.78 (1H, dd), 5.78 (1H, dd), 5.96 (1H, d, J=12 Hz), 7.00-7.03 (2H, t), 7.20-7.48 and 7.67-7.73 (13H, m); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 19.14, 26.24, 26.62, 60.23, 78.72, 82.81, 85.04, 104.89, 112.29, 121.66, 127.60, 127.73, 127.76, 129.53, 129.78, 132.92, 132.96, 134.71, 135.44, 153.21, 193.95; IR 3518 (br), 3070, 2956 (s), 1590 (m), 1427, 1277, 894; Anal. Calcd for $C_{32}H_{36}O_6SiS$: C, 65.93; H, 6.43. Found: C, 66.01; H, 7.57.

1,2-Isopropylidene-3-O-(S-methyldithiocarbonate)-5-O-Diphenyl-t-butylsilyl -b-xylofuranose (**80**).[44]

A round-bottomed flask was charged with 40 g (93.3 mmol) of alcohol **78**, 25 mg of imidazole, and 350 mL of THF. Over a 5-min period, 5.6 g (140 mmol) of a 60% sodium hydride dispersion was added. After the reaction mixture was stirred for 20 min, 21.32 g (280 mmol) of carbon disulfide was added. Stirred was continued for 30 min, 22.5g (159 mmol) of iodomethane was added in a single portion. After 15 min, the solution was filtered and the filtrate is concentrated on a rotary evaporator followed by addition of diethyl ether (350 mL). The organic extract was washed with saturated sodium bicarbonate solution (2 x 100 mL) and water (2 x100mL), and dried over Na_2SO_4. The solvent was evaporated, and the residue was purified by flash chromatography with 30-70 diethyl ether-hexane to yield **80** as a yellow oil (46.7 g,

96.5%): Rf=0.37 (35% THF-hexanes)300 MHz ^{1}H NMR ($CDCl_3$) δ 1.02 (9H, s), 1.08 (3H, s), 1.31 (3H, s), 1.54 (1H, s), 2.49 (3H, s), 3.91 (2H, m), 4.56 (1H, m), 4.65 (1H, d), 5.90 (1H, d), 6.07 (1H, d), 7.32-7.48 and 7.62-7.68 (10H, m); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 19.03, 19.07, 26.22, 26.65, 26.81, 60.18, 79.09, 82.71, 83.88, 104.86, 112.22, 127.67, 127.75, 127.83, 129.71, 132.93, 135.46, 135.60.

1,2-Isopropylidene-3-Deoxy-5-O-Diphenyl-t-butylsilyl-b-xylofuranose (**81**).[31,44b]

(A) 0.85 g (1.5 mmol) of **79** was dissolved in 22 mL of distilled $PhCH_3$ and 49 mg (0.3 mmol) of AIBN and 0.61 mL (2.0 mmol) of n-Bu_3SnH were added. The solution was degassed with argon for 15 min and then heated at 75°C for 3 h. Solvent was evaporated and the residue was chromatographed on silica with ethyl acetate-hexane (80:20) to give **81** as a crystlline solid (0.46 g, 74.1%); m.p. 62.5-64.2°C; Rf=0.65 (35% THF-hexanes); m.p. 62.5-64.2 °C; 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.06 (9H, s), 1.32 (3H, s), 1.52 (1H, s), 1.88 (1H, m), 2.08 (1H, m), 3.79 (2H, m), 4.33 (1H, m), 4.76 (1H, m), 5.82 (1H, d), 7.33-7.46 and 7.64-7.73 (12H, m); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 19.28, 26.69, 26.88, 34.92, 64.68, 78.52, 80.68, 105.71, 111.10, 127.81, 129.59, 129.65, 133.51, 135.64; IR (KBr, film) 3471, 3057, 2854, 1976 (w), 1922, 1589, 1386, 1222 (s), 974, 934, 843, 708, 614; Anal. Calcd for $C_{24}H_{32}O_4Si$, calculated C: 69.86%, H: 7.82; found C: 69.95%, H: 7.87%.

(B) A round-bottomed flask was charged with 47.2 g (91.2 mmol) of **80**, 350 mL of toluene and 37.14 g (127 mmol) of tributyltin hydride. The reaction mixture was heated at reflux until TLC analysis indiated the disappearance of starting materials (6-8 h). During this time the colur of reaction solution was changed from yellow to colorless. Work-up and purification as above method to give **81** (25.8 g, 75.3%), The proton and ^{13}C spectra were identical with that of authenic sample obtained from **79**.

Preparation of diol **82**.

To a stirred THF (5 mL) solution of **81** were added water (3 mL) and HOAc (12 mL) at room temperature. After 12 h, the reaction mixture was neutralized with $NaHCO_3$, and concentrated under reduced pressure. The residue was extracted with CH_2Cl_2, and the extract was washed with brine, dried, and evaporated to leave an oil. The residue was chromatographed on silica with diethyl ether-hexane (85:15) to give **82** as a oil which was a mixture of two aromeric isomers (0.164 g, 40%); Rf=0.26 (35% THF-hexanes); 300 MHz ^1H NMR ($CDCl_3$) δ 1.08 (9H, s), 1.82-2.31 (2H, m), 2.76 (1H, s, br), 3.02 (1H, s, br), 3.48-3.87 (2H, m), 4.21-4.54 (2H, m), 5.30 (1H, d), 7.33-7.48 and 7.62-7.73 (10H, m); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 19.04, 19.10, 26.69, 26.71, 31.93, 33.81, 65.33, 65.81, 65.87, 71.63, 76.50, 79.30, 96.82, 102.37, 127.58, 129.59, 129.91, 133.08, 135.42, 135.48.

1,2-Isopropylidene-3-Deoxy-5-hydroxy-β-xylofuranose (**84**).

Compound **81** (1 g, 2.37 mmol) in THF (6 mL) was added to a 1 M solution of tetra-n-butylammonium fluoride in THF (3 mL, 4.26 mL) and the resultant mixture was stirred at room temperature for 6 h. The mixture was concentrated in vacuo and purified by flash chromatography (9:1 diethyl ether/ hexane) to afford the **84** as a white crystle (0.34 g, 82.9%); Rf=0.23 (35% THF-hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.32 (1H, s), 1.52 (1H, s), 1.90 (2H, m), 2.08 (1H, m), 3.58 (1H, m), 3.88 (1H, m), 4.35 (1H, m), 4.78 (1H, t), 6.83 (1H, d); ; ^{13}C NMR ($CDCl_3$, 300 MHz) δ 26.2, 26.9, 30.39, 60.31, 78.5, 80.0, 105.7, 110.13; IR (KBr, film) 3481 (b), 2966 (m), 1454, 1381 (m), 1266, 1165, 1019 (s), 852, 656; Anal. Calcd for $C_8H_{14}O_6$, calculated C: 55.16%, H: 8.10; found C: 55.33%, H: 8.17%.

1,2-Isopropylidene-3-Deoxy-5-benzyl-b-xylofuranose (**85**).

Sodium hydride (1.79 g, 60% suspension in mineral oil) was washed with hexane, dried, and suspended in DMF (25 mL). Alcohol **84** (6 g, 34.4 mmol) in DMF (10 mL) was added dropwise at 0°C. After the evolution of hydrogen had ceased, benzyl benzyl chloride (4.77 mL, 41.3 mmol) was added and the mixture was allowed to reach room temperature overnight. Water (6 mL) was added and the mixture was extracted with hexane, wash with water, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography (25:75 diethyl ether / hexane) furnished 8.10 g (88.9%) of **85** as an oil. Rf=0.66 (35% THF-hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.30 (1H, s), 1.50 (1H,

s), 1.78 (1H, m), 2.04 (1H, m), 3.58 (2H, m), 3.88 (1H, m), 4.39 (1H, m), 4.57 (2H, s), 4.71 (1H, t), 5.82 (1H, d), 7.32 (5H, m) ; ^{13}C NMR ($CDCl_3$, 300 MHz) δ 26.07, 26.63, 35.10, 70.60, 73.29, 80.27, 77.00, 105.51, 10.92, 127.48, 127.53, 128.22, 137.95; IR 2986 (m), 2934 (m), 1454, 1372 (m), 1214 (m), 1164, 1094 (s), 1024 (s), 851, 738 (m), 698; mass spectrum (EI) 264 (11), 143 (20.3), 91 (100), 69 (21.1), 59 (41); exact mass (EI) for $C_{14}H_{20}O_4$ calcd 264.1364, found 264.1361.

Preparation of diol **86**.

To a stirred dioxane (15 mL) solution of **85** were added HCl (15 mL, 3N) at room temperature. After 15 h, the reaction mixture was neutralized with $NaHCO_3$, and concentrated under reduced pressure. The residue was extracted with CH_2Cl_2, and the extract was washed with brine, dried, and evaporated to leave an oil. The residue was chromatographed on silica with diethyl ether to give **86** as a oil which was a mixture of two aromeric isomers (5.52 g, 81.5%); Rf=0.11 (35% THF-hexanes); 300 MHz ^{13}C NMR ($CDCl_3$, 300 MHz) δ 32.82, 34.07, 71.13, 72.14, 72.38, 73.10, 75.37, 76.39, 77.79, 96.86, 102.57, 127.49, 127.51, 127.64, 127.70, 128.30, 137.23, 137.77; IR 3384 (br.), 2930 (s), 1720 (w), 1453, 1361, 1044 (br.), 738 (m), 698.

Preparation of primary alcohol **87**.

A solution of diol **86** (5.29 g, 23.6 mmol) in absolute ethanol (20 mL) was added to a solution of sodium borohydride in absolute ethanol (30 mL) at 0°C. After stirring for 1 h, acetone (20 mL) was added with vigorous stirring, followed by acetic acid until no gas was evolved. After removal of the solvent in vacuo, the residue was dissolved in a mixture of ethyl acetate and saturated aqueous ammonium chloride. Saturated sodium disulfate was added until the aqueous layer was about pH 5, then extracted with ethyl acetate (3 x 50 mL), and the combined organic layers were dried. Removal of the solvent in vacuo provided the triol as an oil.

A solution of triol, 2,2-dimethoxypropane (3.0 g, 30.8 mmol), and TsOH (25 mg) in Me_2CO (8 mL) was stirred at room temperature for 8 h. After addition of CH_2Cl_2 (25 mL), the solution was washed successively with aqueous $NaHCO_3$ and water, dried. The solvent was evaporated under reduced pressure and chromatographed on a silica gel column to give the **87** as an oil (3.38 g, 54.0%); 300 MHz ^1H NMR ($CDCl_3$) δ 1.33 (3H, s), 1.39 (3H, s), 1.74 (2H, t), 3.14 (1H, d), 3.44 (2H, d), 3.55 (1H, t), 4.95 (1H, m), 4.05 (1H, m), 4.24 (1H, q), 4.53 (2H, s), 7.22-7.37 (5H, m); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 25.51, 26.67, 35.74, 68.72, 69.25, 73.11, 73.85, 74.21, 76.57, 108.81, 127.49, 128.17, 137.80.

Preparation of compound **88**.

To a solution of the alcohol **87** (1.25 g, 4.7 mmol) and 2,6-dimethyllutidine (0.93 mL, 7.98 mmol) in 11 mL of CH_2Cl_2

was added tert-butyldimethylsilyl trifluoromethanesulfonate (1.51 mL, 6.57 mmol) over 2 min at 0°C. The reaction mixture was stirred for 5 h at room temperature and was diluted with CH_2Cl_2, washed with $NaHCO_3$, dried with Na_2SO_4. Flash chromatography through silica gel afforded **88** (1.77 g, 100%) as an oil; 300 MHz ^1H NMR ($CDCl_3$) δ 0.06 (6H, s), 0.89 (9H, s), 1.18-1.36 (1H, m), 1.40 (3H, s), 1.46 (3H, s), 1.51 (1H, m), 2.62 (1H, s), 3.36 (1H, m), 3.51 (3H, m), 4.0 (2H, m), 4.55 (2H, q), 7.22-7.34 (5H, m); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 19.62, 25.79, 29.15, 29.77, 65.75, 67.87, 69.31, 73.24, 98.63, 127.45, 127.54, 128.17, 137.93.

Preparation of primary alcohol **89**.

Compound **88** (1.2 g, 3.15 mmol) was hydrogenated in absolute ethanol (13 mL) in the presence of 10% Pd-C (500 mg) at ordinary pressure and temperature for overnight. After removal of the catalyst by filtration, evaporation of the solvent left the oily alcohol **89** (0.89 g, 97.5%), 300 MHz ^1H NMR ($CDCl_3$) δ 0.06 (6H, s), 0.89 (9H, s), 1.19-1.55 (2H, m), 1,40 (3H, s), 1.46 (3H, s), 2.62 (1H, s), 3.41-3.70 (4H, m), 3.98 (2H, m); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 18.22, 19.75, 25.79, 29.15, 29.77, 66.94, 66.77, 69.29, 69.54, 98.55.

2,4-Dihydroxyacetonide-5-t-butyldimethylsiloxypentanoic acid (**90**).[46]

Primary alcohol **89** (893 g, 3.06 mmol) was dissolved in 8.8 mL of carbon tetrachloride, 8.8 mL of acetonitrile, and

13.3 mL of water and cooled to 0°C. Ruthenium (III) chloride trihydrate (22 mg, 0.11 mmol) was added, followed by sodium metaperiodate (2.63 g, 12.3 mmol) over 5 min. The reaction mixture was allowed to stir for 3 h at room temperature, and quenched with 30 mL of dichloromethane. The aqueous layer was separated and extracted with dichloromethane (3 x 30 mL). The organic extracts were dried and filtered through Celite 545. The dark solution was concentrated and then purified by silica gel chromatography (pure ethyl acetate) to provide **90** as an oil (0.75 g, 81.0%); 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.06 (6H, s), 0.89 (9H, s), 1.22-1.55 (2H, m), 1,48 (6H, s), 2.04 (1H, t), 3.61 (1H, m), 3.69(1H, q), 3.95-4.26 (2H, m), 4.54 (1H, q), 9.25 (1H, s); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 18.22, 19.41, 25.67, 29.53, 30.13, 66.29, 68.04, 69.50, 99.45, 174.58.

Preparation of ylide **68**.[47]

To a solution of acid (**28**; 469 mg, 1.54 mmol) intetrahydrofuran (4.5 mL) was added 1,1-carbonyldiimidazole (287 mg, 1.77 mmol). After 20 min, when evolution of carbon dioxide had ceased, the mixture was added to the Wittig reagent geneaated from methyltriphenylphosphonium bromide (1.734 g, 4.42 mmol) and 2.5 M butyllithium (1.85 mL, 4.62 mmol) in benzene at room temperature. After the reaction mixture was stirred for 2 h, a solution of ammonium chloride (20 mL) was added, and the benzene layer was separated, washed with water, dried, and evaporated. The residue was subjected to column chromatography, using 3:7 hexane-diethyl

ether, to give pure **68** (466 mg, 52.0%) as a white foma; 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.06 (6H, s), 0.88 (9H, s), 1.21-1.43 (2H, m), 1,48 (6H, s), 2.10 (1H, t), 3.53 (1H, m), 3.68(1H, q), 3.95-4.35 (2H, m), 7.40-7.75 (15H, m); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 18.33, 19.77, 25.88, 30.06, 32.32, 47.56, 49.01, 67.17, 70.45, 73.37, 73.53, 98.57, 128.63, 128.80, 131.89, 131.93, 133.09, 191.57.

1-*tert*-butyldimethylsiloxy-2-propyne (**93**).

A solution of 5.6 g (0.1 mol) of propargyl alcohol (**92**), 18.1 g (0.12 mol) of t-$BuMe_2SiCl$, and 17.0 g (0.25 mol) of imidazole in 12 mL of DMF was stirred for 15 h at room temperature. The mixture was then diluted with 90 mL of hexane and washed (3 x 35 mL) with water, dried, evaporated. Distillation of the residue gave 13.8 g (81.2%) of **93**: bp 60-62.5 ^{o}C (5.7 mm); 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.10 (6H, s), 0.89 (9H, s), 2.36 (1H, t), 4.22 (2H, d, J= 2 Hz); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 18.09, 25.64, 51.29, 72.75,82.23, 213.42.

1-*tert*-butyldimethylsiloxy-2-pentyn-5-ol (**94**).[48]

A solution of n-butyllithium in hexane (3.05 mL, 5.87 mmol) was added to a THF solution (2 mL) of **93** (1 g, 5.87 mmol) at -78^{o}C, and the mixture was stirred for 15 min. Borontrifluoride etherate (0.7 mL) was added to the solution and the stirring was continued for 15 min. Then, a THF solution of ethylene oxide (0.51 g, 11,7 mmol) was added, and after stirring for 30 min, the reaction was quenched by

adding aqueous ammonium chloride. The organic layer was extracted with diethyl ether, dried, evaporated. Column chromatography of the residue, using 60:40 hexane-diethyl ether, gave pure **94** (0.4 g, 32%) as a liquid; 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.11 (6H, s), 0.89 (9H, s), 2.47 (2H, m), 2.98 (1H, s), 3.58 (2H, q), 4.19 (2H, t); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 18.23, 22.97, 25.76, 51.85, 60.80, 80.19, 81.97; Anal. Calcd for $C_{11}H_{22}O_2Si$, calculated C: 61.62%, H: 10.34; found C: 61.74%, H: 10.27%.

1-*tert*-butyldimethylsiloxy-5-(tert-butyldimethylsil)oxy-2-pentyn (**95**)

60% NaH dispersion (78 mg, 3.26 mmol) was added to a stirred solution of alcohol **94** (1 g, 4.66 mmol) in dimethylformamide (DMF) (15 mL) at room temperature. After 30 min, 4-methoxybenzyl chloride (MPMCl) (511 mg, 3.26 mmol) was added and the mixture was stirred for 5 h. The reaction mixture was poured into ice aqueous NH_4Cl and extracted with diethyl ether. The combined extract was washed with brine, dried ($MgSO_4$), and evaporated to leave an oil, which was chromatographed on silica gel column with n-hexane/ether (85:15) as eluant to give compound **95** as an oil (530 mg, 50.7%); 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.06 (3H, s), 0.84 (9H, s), 2.34 (2H, m), 3.63 (2H, t), 3.69 (3H, s), 4.02 (2H, t), 4.52 (3H, s)6.78 (2H, d), 7.19 (2H, d); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 18.2, 23.4, 26.1, 52.4, 55.7, 57.2, 62.0, 68.2, 71.6, 84.0, 114.1, 129.2, 129.8, 159.3.

5-(4-methoxybenzyl)-2-pentyn-1-ol (**96**).

Method A: Compound **95** (180 mg) was desilylated as described for the preparation of alcohol **84** to afford compound **96** as an oil (68 mg, 58.7%); Rf=0.28 (35% THF-hexanes), 300 MHz ^{1}H NMR ($CDCl_3$) δ 2.48 (2H, m), 3.02 (1H, s), 3.52 (2H, t), 3.77(3H, s), 4.16 (2H, t), 4.45 (2H, s), 6.86 (2H, d), 7.24 (2H, d); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 19.87, 50.69, 55.02, 67.70, 72.32, 79.54, 82.44, 113.60, 129.21, 129.71, 159.03; IR 3416 (br.), 2864 (m), 2225 (w), 1612, 1513, 1362, 1248 (s), 1094, 1031(m), 822; mass spectrum (EI) 189 (18.2), 171 (9.9), 135 (10), 121 (100), 91 (7.8), 78 (28.3), 77 (22.5), 51 (15.7); exact mass (EI) for $C_{13}H_{16}O_3$ calcd 220.1099, obsd 220.1127.

Method B[49]: A solution of **98** (16.77 g, 88.15 mmol) and THF (300 mL) was treated dropwise at -78°C with BuLi (35.3 mL of a 2.5 M solution in hexane, 88.15 mmol), and the reaction mixture was allowed to warm to room temperature overnight. Paraformaldehyde (3.44 g, 114.6 mmol, dried in vacuo for 30 h) was added followed by THF (150 mL). The resulting mixture was heated at reflux for 3 h, and after cooling to room temperature, was poured into brine (80 mL). The organic layer was washed with saturated aqueous NH_4Cl (2 x 30 mL), dried, and evaporated. Purification by flash chromatography provided alcohol **96** (17.01 g, 87.6%); the IR, proton and ^{13}C spectra were identical with that of sample obtained by the method B.

1-O-(4-methoxybenzyl)-3-butyn (**98**):

60% NaH dispersion (5.75 g, 143 mmol) was added to a stirred solution of 3-butyn-1-ol (**97**) (9.26 g, 132 mmol) in dimethylformamide (DMF) (30 mL) at 0°C. After 30 min, 4-methoxybenzyl chloride (MPMCl) (18 g, 115 mmol) was added and the mixture was stirred for 5 h. The work-up and purification procedure was same as decribed for the preparation of **95** to afford compound **98** as an oil (19.12 g, 87.5%); Rf=0.48 (35% THF-hexanes) 300 MHz ^{1}H NMR ($CDCl_3$) δ Rf=0.61 (35% THF-hexanes) 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.98 (1H, t), 2.45 (2H, m), 3.53 (2H, t), 3.74(3H, s), 4.45 (2H, s), 6.85 (2H, t), 7.24 (2H, t); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 19.61, 54.90, 67.95, 69.20, 72.32, 81.13, 113.53, 129.05, 129.85, 158.99; IR 3291 (m), 2862, 1612, 1513 (s), 1361 (w), 1248 (s), 1098, 1034 (m), 822; Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.68; H, 7.47.

5-(4-methoxybenzyl)-2-*trans*-pentene-1-ol (**99**).[50]

To a solution of lithium aluminum hydride (3.5 g, 92.6 mmol) in dry diethyl ether (200 mL) was added solution of alcohol **96** (17.0 g, 77.2 mmol) in dry diethyl ether (25 mL) at 0° C. The reaction mixture was allowed to room temperature and stirred for 5 h, and then was cooled. Water was added dropwise over a period of 30 min to the stirred reaction mixture until no bubble was observed. A solution of ammonium chloride (150 mL) was added, and the mixture was passed

Celite 506. The organic layer was washed with water, dried, and evaporated. The residue was subjected to column chromatography, using 5:5 hexane-diethyl ether, to give pure compound **99** (14.57 g, 85.6%) as a oil; 300 MHz ^{1}H NMR ($CDCl_3$) δ 2.33 (3H, m), 3.46 (2H, t), 3.77 (3H, s), 4.02 (2H, s), 4.42 (2H, s), 5.66 (2H, t), 6.86 (2H, m), 7.25 (2H, t); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 32.46, 55.09, 63.22, 69.15, 72.36, 113.60, 129.17, 130.19, 130.92, 159.00; IR 3404 (br.), 2933, 2858, 1612, 1513 (s), 1463, 1301, 1248 (s), 1095, 1034, 971, 820; mass spectrum (EI) 150 (8.1), 136 (8.4), 122 (12.4), 121 (100), 78 (9.7); exact mass (EI) for $C_{13}H_{18}O_3$ calcd, 222.1255, obsd 222.1244.

(2s-*trans*)-5-(4-methoxybenzyl)-ethyloxranemethanol (**100**).[51]

Titanum (IV) isopropoxide (1.62 g, 5.68 mmol) was added to a suspension of 4-A powdered molecular sieves (2 g), CH_2Cl_2 (130 mL), and diethyl D-tartrate (1.52 g, 7.38 mmol) at -24 ^{o}C. After 20 min at -24 ^{o}C, 3.0 M anhyhydrous *tert*-butylhydroperoxide (37.85 mL, 113.6 mmol) was added. After another 20 min, the alcohol **99** was added slowly by syringe. The reaction mixture was stirred for 2 h at -24 ^{o}C, and then flask was sealed and placed in the freezer (-22 ^{o}C) for 24 h. TLC showed no starting material, so it was quenched with water (25 mL) and allowed to warm to room temperature. Aqueous NaOH (30%) saturated with NaCl (20 mL) was added. After 20 min, the solution was passed through the Celite to obtain clean solution. The layer were separated, and the

aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organics were dried, concentrated, and chromatographed, using hexane-ethyl acetate 4:6, to give desired compound **100** as an oil (11.40 g, 84.7%); 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.82 (2H, s), 2.91 (1H, m), 3.01 (1H, m), 3.32 (1H, s), 3.54 (3H, m), 3.76 (4H, t), 4.41 (2H, m), 6.85 (2H, t), 7.23 (2H, d); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 31.46, 53.41, 54.80, 54.82, 58.30, 61.53, 66.19, 72.26, 113.40, 128.90, 129.87, 158.80; IR 3432 (br.), 2933, 2862, 1612, 1513 (s), 1363, 1248 (s), 1098 (s), 1033, 820; mass spectrum (EI) 189 (11.2), 137 (52.3), 136 (12.3), 121 (100), 78 (13.4), 77 (12.5); exact mass (EI) for $C_{13}H_{18}O_4$ calcd, 238.1205, obsd 238.1170.

Preparation of diol **101**.[52]

A solution of epoxy alcohol **100** (16.0 g, 67.1 mmol) in hexane (20 mL) was added dropwise to a solution of trimethylaluminium (0.2 M, 100 mL, 201 mmol) in hexane at 0 ^{o}C. After stirring for 40 min, the reaction mixture was diluted with CH_2Cl_2 (50 mL), and water (20 mL). After stirring another 40 min at room temperature the mixture was filtered and the remaining solid was washed with ether (3 x 60 mL). The combined organic solution was dried and concentrated. Purification of the residue by silica gel column chromatography provided 1,2-diol **101** (14.2 g, 83.1%) as a colourless oil; 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.87 (3H, d), 1.52 (1H, m), 1.77 (2H, m), 3.5 (6H, m), 3.77 (3H, s), 3.98

(1H, s), 4.42 (2H, s), 6.86 (2H, t), 7.24 (2H, d); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 15.97, 32.45, 33.46, 54.97, 55.00, 64.43, 67.76, 72.50, 75.80, 113.58, 129.17, 129.84, 159.00; IR 3395 (br.), 2932, 2872, 1612, 1513, 1463, 1364, 1302, 1248, 1086 (s), 1035, 821,756, 733.

Preparation of secondary alcohol **102**.

1,2-Diol **101** (5.24 g, 20.6 mmol) was mono-benzylated as described for the preparation of compound **85** to afford primary alcohol (0.8 g, 11.6%); and the secondary alcohol **102** as an oil (3.85 g, 55.9%); 300 MHz ^1H NMR ($CDCl_3$) δ 0.89 (3H, d), 1.52 (1H, m), 1.81 (2H, m), 2.91 (1H, s), 3.39-3.65 (5H, m), 3.78 (3H, s), 4.42 (2H, s), 4.54 (2H, s), 6.85 (2H, d), 7.23 (2H, d), 7.32 (5H, m); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 15.90, 32.27, 33.47, 55.18, 55.16, 67.88, 72.53, 73.28, 74.21, 113.69, 127.63, 128.34, 129.20, 130.33, 138.06, 159.07.

Preparation of compound **103**.

The secondary alcohol **102** (3.8 g, 11.4 mmol) was silylated as described for the preparation of compound **93** by silica gel column chromatography to afford compound **103** (5.0 g, 100 %) as an oil; 300 MHz ^1H NMR ($CDCl_3$) δ 0.03 (6H, d), 0.88 (12H, m), 1.41 (1H, m), 1.81 (2H, m), 3.35-3.54 (3H, m), 3.72 (3H, s), 4.39 (2H, d), 4.56 (2H, d), 6.83 (2H, d), 7.23 (2H, d), 7.29 (5H, m); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 16.16, 18.06, 25.82, 30.88, 33.59, 54.96, 54.99, 68.47, 72.34,

72.78, 73.11, 75.25, 113.56, 127.29, 127.41, 128.13, 129.03, 130.61, 138.33, 158.94.

Preparation of primary alcohol **104**.[53]

To a stirred solution of the MPM ether **103** (1 g, 2.23 mmol) in CH_2Cl_2 (6 mL) and water (0.3 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (632 g, 2.78 mmol). The mixture was stirred at room temperature for 40 min, then diluted with CH_2Cl_2 (25 mL), washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), evaporated to leave an crude oil. To a solution of the crude oil in ethanol (25 mL) was added with solid sodium borohydride (110 mg, 2.9 mmol) at 0 ^oC and the mixture was allowed to warm to room temperature. The mixture was neutralized with diluted AcOH, concentrated under reduced pressure, and diluted with water. Extraction with ether and the usual workup delivered the crude alcohol **104**, which was purified by flash chromatography (1:1 hexane-ether) to afford pure compound **104** (0.65 g, 89.3%); 300 MHz ^1H NMR ($CDCl_3$) δ 0.06 (6H, d), 0.88 (9H, s), 0.95 (3H, d), 1.58 (2H, m), 1.92 (1H, m), 2.68 (1H, s), 3.49 (3H, m), 3.61-3.81 (2H, m), 4.49 (2H, d), 7.31 (5H, m); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 18.11, 19.90, 27.62, 35.03, 35.35, 61.65, 74.49, 75.01, 77.00, 129.27, 129.36, 130.03, 139.93.

Preparation of ester **105**.[54]

The alcohol **104** (5.28 g, 16.2 mmol) was oxidized as described for the preparation of compound **90** to afford a acid as a crude oil; ^{13}C NMR ($CDCl_3$, 300 MHz) δ 16.90, 18.15, 25.89, 29.72, 30.34, 33.42, 36.13, 72.61, 73.34, 74.59, 127.66, 128.33, 138.15, 179.85. Esterification of the acid was carried out with diazomethane (generated from 8 g of diazald and 2.2 g of potassium hydroxide in 80 mL of 8:1 ethanol/ether and poured ioto the reaction flask) in ether (20 mL) at 0 °C. Nitrogen was bubbled through the yellow reaction mixture until the solution became clear. Evaporation and silica gel chromatography (25:75 ether/hexane) afforded ester **105** as an oil (4.63 g, 81.2%); 300 MHz ^1H NMR ($CDCl_3$) δ 0.03 (6H, d), 0.87 (9H, s), 0.96 (3H, d), 2.11 (1H, q), 2.24 (1H, m), 2.49 (1H, m), 3.39 (2H, m), 3.65 (3H, s), 3.72 (1H, q), 4.49 (2H, d), 7.33 (5H, m); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 16.85, 18.10, 25.73, 25.84, 33.57, 35.98, 51.30, 51.34, 27.65, 73.25, 74.53, 127.49, 127.55, 128.26, 138.19, 173.93.

Preparation of primary alcohol **106**.

The ester **105** (100 mg, 0.281 mmol) was hydrogenated as described for the preparation of compound **89** to afford alcohol **106** as an oil (47 mg, 61.0%); 300 MHz ^1H NMR ($CDCl_3$) δ 0.08 (6H, s), 0.90 (9H, s), 2.19 (1H, q), 2.29 (2H, m), 2.58 (1H, dd), 3.41-3.63 (3H, m), 3.68 (3H, s); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 16.94, 18.03, 25.74, 32.33, 36.11, 51.54, 51.57, 63.80, 75.53, 128.27, 174.30.

Preparation of aldehyde **69**.[55]

A mixture of the alcohol **106** (320 mg, 1.16 mmol) and Dess-Martin periodinane (i.42 g, 3.4 mmol) was stirred in 5 mL of dichloromethane for 6 h. The cloudy mixture was quenched with saturated aqueous sodium thiosulfate (7 mL), diluted with ethyl acetate (8 mL), and stirred until the organic layer became clear. The organic solution was dried, concentrated, and purified by flash chromatography (2:8 ether/hexane) to furnish the aldehyde **69** as an oil (287 mg, 87.5%); 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.08 (6H, s), 0.93 (9H, s), 1.04 (3H, d), 2.20 (1H, q), 2.45 (2H, m), 3.65 (3H, s), 3.87 (1H, d), 9.58 (1H, s); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 16.32, 17.98, 25.54, 32.99, 35.51, 51.28, 51.32, 80.44, 172.71, 203.24.

Preparation of compound **67**.[56]

Aldehyde **69** (180 mg, 0.32 mmol) and Wittig compound **68** (110 mg, 0.40 mmol) were treated with toluene (6 mL) under reflux for 15 h. Evaporation and silica gel chromatography (13:77 ether/hexane) afforded acid **67** as an oil (57 mg, 32%); 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.02 (12H, t), 0.88 (9H, s), 0.94 (9H, s), 0.98 (3H, d), 1.30 (2H, m), 1.44 (3H, s), 1.47 (3H, s), 1.85 (1H, d), 2.15 (2H, m), 2.42 (1H, m), 3.5 (1H, q), 3.65 (3H, s), 3.99 (1H, m), 4.26 (1H, t), 4.42 (1H, m), 6.79 (1H, m), 6.95 (1H, m); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 16.51, 18.12, 18.29, 19.43, 25.81, 29.74, 36.02, 36.05, 51.45,

51.49, 66.66, 69.59, 73.95, 74.89, 99.90, 124.02, 148.61, 173.36, 197.84.

Preparation of α,β-unsaturated ketone **108**.

To a solution of 3,4-dihydro-2H-pyran **107** (12.7 g, 151 mmol)in 70 mL of water was added HCl (4.6 mmol, 4.6 mL of one mol solution). After about two hours, the mixture was quenched with saturated $NaNH_4$ and the aqueous layer was extracted 4 times with ethyl acetate. The organic phase was dried over MgSO4 and concentrated in vacuo to give crude aldehyde, which (13 g, 127 mmol) was placed into a 250 mL RBF along with a magnetic stirrer. The methyl ketone Wittig reagent (43 g, 135 mmol) was dissolved in CH_2Cl_2 (100 mL) and placeed into a large addition funnel. CH_2Cl_2 (50 mL) was added to the aldehyde in the reaction flask and ylide solution was slowly added to the reaction mixture. The reaction was allowed to proceed overnight and was extracted with H_2O (2 x 100 mL). the organic layer was dried with Na_2SO_4 and concentrated in vacuo. Column chromatography of the residue produced a 1,98 g of colorless oil (8.7 mmol, 25%); 300 MHz ^1H NMR ($CDCl_3$) δ 1.48-1.88 (12H, m), 2.25 (5H, m), 3.33-3.55 (2H, m), 3.71-3.91 2H, m), 4.57 (1H, s), 6.08 (1H, d), 6.81 (1H, m); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 19.70, 24.95, 25.53, 26.86, 29.31, 30.79, 32.30, 62.35, 67.11, 98.90, 131.50, 148.27, 199.1.

Methyl-(s)-7-oxo-6-octenoate (**109**).

The protected alcohol **108** (0.2 g, 0.88 mmol) was oxidized and esterificated as described for **105** to give, after flash chromatography, ester **109** (0.118 g, 0.693 mmol) as a colorless oil; 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.9 (2H, m), 1.82 (2H, m), 2.26 (3H, s), 2.37 (2H, t), 3.69 (1H, s), 6.16 (1H, d), 6.79 (1H, m); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 23.16, 26.75, 31.54, 33.12, 51.51, 131.74, 146.67, 173.38, 199.7.

3-butanal-2-cyclohexnenone (**131**).[63,64]

To oxalyl chloride (0.84 g, 6.6 mmol) in methylene chloride (50 mL) was added DMSO (1.034 g, 13.2 mmol) over a 5-min period with concomitant gas at $-78^{0}C$, and after 10 min at $-78^{0}C$, the alcohol (1.0 g, 6.02 mmol) in 12 ml of methylene chloride was added over 10 min, resulting in a cloudy solution which was stirred for 20 min. To this was added 4.2 mL (30.1 mmol) of triethylamine, and the mixture was stirred for 30 min at $-78^{0}C$. The cooling bath was removed and water (20 mL) was added. Extraction with methylene chloride (50 mL), drying over anhydrous $MgSO_4$, and flash chromatography afforded the aldehyde **131** (0.988 g, 83.3 %) as an oil, which was identical to that prepared by Godlesky and co-workers.[64b]

(+,-)-octahydro-8-hydroxy-1-(2H)-naphthalenone (**132**).

A solution of the aldehyde **131** (0.32 g, 1.93 mmol) was dissolved in benzene (0.2 M, 10 mL) in a pear flask equipped with a condenser and oil bath. To the flask was added AIBN

(0.10 eq, 32 mg) and TBTH (1.12 g, 3.85 mmol), the solution was carefully degassed by bubbling with argon for 0.5 h. The reaction was heated at 80^0C (bath temperature) in a manner that the level of the oil bath was lower than the level of the solution. After 12 h, thin layer chromatography inicated no UV active staring aldehyde remaining and the reaction was complete. solvents were removed under reduced pressure and the crude oil was subjected to flash chromatography (18 g of silica gel) to isolate an thick oil **132** (0.294 g, 81.22%) using 230 mL of hex/ether-30:70 as solvents: Rf=0.35 (35% THF-hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 4.19 (t, 1H), 2.46 (s, 1H), 2.45 (m, 2H), 2.32 (m, 2H), 1.86-2.07 (m, 2H), 1.79 (m, 2H), 1.63 (m, 3H), 1.44 (m, 3H; ^{13}C NMR ($CDCl_3$, 300 MHz) δ 213.47, 66.79, 58.88, 39.74, 37.23, 32.67, 28.82, 27.76, 24.33, 20.03; IR (neat oil on NaCl plates) 3407 (brod. s), 2932 (s), 2864, 1705 (s), 1447, 1128, 1050, 971, 734 cm^{-1}; HRMS calcd: for $C_{10}H_{16}O_2$, 168.1150, found: 168.1125; Anal. Calcd: C, 71.39%, H, 9.59; found: C, 71.31%, H, 9.91%.

We used hexane, ethyl alcohol, 2-propanol as solvents to try obtain crystals from alcohol **131**, unfortunately, all of them failed.

(+,-)-octahydro-8-oxo-papabrobenzeneester-1-(2H)-naphthalenone (**133**).[65]

Thionyl chloride (5.0 mL, 62.2 mmol) was added to 4-Bromobenzoic acid and refluxed overnight at 85^0C to give clear solution. The solvent was removed by rotary

evaporation, followed by full pump, to give the desired compound as colorless needles. 4-Bromobenzoyl chloride (0.78g, 3.57 mmol) was dissolved in 10 mL of pyridine and THF (1:1) and a solution of alcohol **132** (0.2 g, 1.19 mmol) in 2 mL of pyridine was added to the flask dropwise. The mixture was stirred for 6 h and was then poured into 10 mL of water and extracted with methylene chloride (3 x 45 mL). The extract was washed with sodium bicarbonate solution, dried ($MgSO_4$). Evaporation of the solvent and flash chromatography (25 g of silica gel) obtained ester **133** (0.32 g, 76.4%,) using 310 mL of hex/ether-65:45 as solvents: Rf=0.58 (35% THF-hexanes); 300 MHz ^1H NMR ($CDCl_3$) δ 7.87 (d, 2H),7.56 (d, 2H), 5.60 (d, 1H), 2.84 (t, 1H), 2.45 (m, 2H), 2.26 (m, 1H), 2.1-1.32 (m, 10H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ210.32, 164.40, 131.12, 130.55, 128.87, 127.45, 69.97, 54.09, 40.46, 36.47, 28.66, 27.58, 27.38, 22.91, 20.16. Recrystallization from 30 mL of ethanol at room temperature (one week) obtained desired ester as colorless crystal, m.p. 120.8-121.7 ^0C.

4a-methyl-4,4a,5,6,7,8-hexahydronaphthelen-2-one (**134**).

Was prepared by the method of Heathcock and coworkers.[68]

Alkene **135**; dialcohol **136** and alcohol **137**.

Were identical to that prepared by Becker and co-workers.[67]

(+,-)-4-butanal-4-methyl-2-cyclohexenone (**138**).[64]

Prepared by Swern oxidationxx of **137**; Rf=0.37 (35% THF-hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 9.78 (t, 1H), 6.70 (d, 1H), 5.86 (d, 1H), 2.38-2.55 (m, 4H), 1.98 (m, 1H), 1.79 (m, 1H), 1.67 (m, 2H), 1.48 (m, 2H), 1.65 (s, 3H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 202.24, 199.68, 159.07, 127.93, 44.50, 40.65, 36.01, 34.52, 34.47, 25.09, 17.13; IR (neat oil on NaCl plates) 3340, 2955, 1723, 1681, 1391, 1120, 806 cm^{-1}; HRMS calcd: for $C_{10}H_{17}O_2$ (M+1) 181.1228, found: 181.1262; Anal. Calcd: C, 73.30%, H, 8.95; found: C, 72.90%, H, 9.05%.

(+,-)-endo-5-hydroxy-1-methylbicyclo[4.3.1]decan-7-one (**139**).

Rf=0.43 (35% THF-hexanes): 300 MHz ^{1}H NMR ($CDCl_3$) δ 3.61 (m, 2H), 2.72 (q, 1H), 2.50 (m, 2H), 2.14 (m, 1H), 1.20-1.89 (m, 9H), 0.98 (s, 3H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 199.11, 75.24, 50.49, 38.20, 37.61, 37.15, 37.02, 35.81, 31.91, 31.17, 19.55; IR (KBr film) 3410 (brod. s), 2932 (m), 2860, 1701 (s), 1448 (w), 1313, 1227, 1057 (m) cm^{-1}; Exact mass for $C_{11}H_{18}O_2$, calc. 182.1306, found: 182.1320; Anal. Calcd: C, 72.49%, H, 9.95; found: C, 72.35%, H, 10.06%.

We used 3 mL of 2-propanol / hexane (1:1) as a solvent to recrystallize alcohol **139** at room temperature and obtained the desired coulorless crystal in four days, m.p. 67.2-68.5^{0}C.

Deuterated **131** (**140**).

It was indistinguishable from **131** by TLC, capillary GC and spectroscopic methods except it had a reduction in the

tertiary ^{13}C NMR resonance at 37.2 PPM and a loss of the resonance in the ^{1}H NMR at 1.86-2.07 PPM which now integrated to ^{1}H instad of 2H.

3-(4'-t-butyldimethylsiloxybutane)-2-cyclohexenone (**141**).

Prepared by standard methods from the known alcohol.[64] Rf=0.60 (35% THF-hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 5.87 (s, 1H), 3.62 (t, 2H), 2.21-2.39 (m, 6H), 1.98 (m, 2H), 1.54 (m, 4H), 0.89 (s, 9H), 0.049 (s, 6H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 199.80, 166.35, 125.62, 62.52, 37.71, 37.27, 32.18, 29.51, 25.86, 23.16, 22.63, 18.23; IR (neat oil on NaCl plates) 2931, 2858, 1672, 1462, 1255, 1102, 836, 776 cm^{-1}; Anal. for $C_{16}H_{30}O_2Si$, Calcd: C, 68.03%, H, 10.71; found: C, 68.01%, H, 10.92%.

Decyl Aldehyde (**142**).

Was commercially avaiable from Aldrich Chemical Co. and used "as is".

3-(4'-t-butyldimethylsiloxybutane)-2-cyclohexanone (**143**).

Rf=0.66 (35% THF-hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 3.60 (t, 2H), 2.18-2.47 (m.4H), 1.5-2.08 (m, 7H), 1.18-1.41 (m, 4H), 0.89 (t, 9H), 0.045 (s, 6H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 213.42, 62.91, 48.13, 41.45, 39.02, 36.34, 32.76, 31.20, 25.90, 25.23, 22.86, 18.28; IR (neat oil on NaCl plates) 2930, 2858, 1715, 1462, 1255, 1100, 836, 776 cm^{-1}; Anal. for

$C_{16}H_{32}O_2Si$, Calcd: C, 67.54%, H, 11.34; found: C, 67.43%, H, 11.52%.

Decyl Alcohol (**144**).

Was compared with a commercially available sample from Aldrich Chemical Co.

3-hydroxy-1-(4'-t-butyldimethylsiloxybutane)cyclohexene (**155**).

The keton **141** (0.6 g, 2.12 mmol) was reduced as described for the preparation of compound **104** to afford alcohol **155** as an oil (0.6 g, 99.3%); 300 MHz ^1H NMR ($CDCl_3$) δ 0.02 (6H, s), 0.86 (9H, s), 1.34-1.56 (6H, m), 1.68-1.97 (6H, m), 2.42 (1H, s), 3.56 (2H, t), 4.13 (1H, d), 5.44 (1H, s); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 18.27, 19.15, 23.60, 25.91, 28.34, 31.89, 32.39, 37.23, 62.96, 65.71, 123.98; Anal. for $C_{16}H_{32}O_2Si$, Calcd: C, 67.57%, H, 11.31; found: C, 67.58%, H, 11.57%.

3-Phenylthio-1-(4'-butyldimethylsiloxybutane)cyclohexene (**156**).[72]

To a solution of alcohol **155** (3.1 g, 10.9 mmol) and triethylamine (1.65 g, 16.3mmol) in 30 mL of methylene chloride at -20 ^oC was added methanesulfonyl chloride (1.37 g, 12 mmol). The mixture was stirred for 1 h while maintaing a temperature of between -20 and -10 ^oC. A second solution of lithium thiophenoxide was prepared by the action of n-

butyllithium (5.01 mL of a 2.5 M solution in hexane, 12.5 mmol) on thiophenol (1.38 g, 12.5 mmol) in 30 mL of THF. The lithium thiophenoxide solution was added to the first solution at -15 °C, and the reaction was then allowed to warm to room temperature. After stirring overnight, the reaction mixture was partitioned between 300 mL of ether and 150 mL of saturated ammonium chloride. The organic layer was separated and dried, and the solvent was removed in vacuo. The flash chromatography afforded the product **156** (2.3 g, 54.5 %) as an oil; 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.02 (6H, s), 0.85 (9H, s), 1.35-1.58 (6H, m), 1.68-1.96 (6H, m), 3.35 (2H, s), 3.54 (2H, t), 3.81 (1H, s), 5.47 (1H, s), 7.12-7.44 (5H, m); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 20.0, 23.2, 25.8, 26.1, 27.9, 28.2, 35.5, 37.8, 44.7, 63.2, 120.9, 126.4, 128.7, 131.1, 136.1, 141.7.

1-Butanal-3-(phenylthio)cyclohexene (**157**).

The protected alcohol **156** was deprotected and oxidized as described for **84** and **138** to give aldehyde **157** as a colorless oil.

Alcohol **158**: 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.39-2.15 (12H, m), 2.41 (1H, s), 3.6 (2H, t), 3.88 (1H, s), 5.51 (1H, d), 7.15-7.30 (3H, m), 7.39 (2H, t); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 19.67, 23.68, 25.69, 28.21, 28.73, 32.28, 37.51, 44.55, 62.56, 120.94, 126.45, 128.79, 131.16, 136.14, 141.76.

Aldehyde **157**: 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.51-2.15 (12H, m), 2.38 (2H, t), 3.88 (1H, d), 5.51 (1H, d), 7.15-7.32 (3H, m), 7.4 (2H, m), 9.75 (1H, s); ^{13}C NMR ($CDCl_3$, 300 MHz) δ

19.65, 19.88, 28.05, 28.71, 36.95, 43.16, 44.46, 121.99, 126.55, 128.79, 131.33, 135.98, 140.64, 202.29.

3-Phenylthio-6-methyl-6-(4'-t-butyldimethylsiloxybutane)cyclohexene (**160**).

The keton **159** was reduced as described for the preparation of compound **104** to afford an alcohol as an oil ; 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.02 (6H, s), 0.86 (9H, s), 0.93 (3H, s), 1.2-1.99 (10H, m), 3.57 (2H, t), 4.08 (1H, s), 5.5 (2H, m); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 20.15, 20.37, 25.92, 26.57, 29.21, 30.72, 33.53, 33.57, 42.04, 65.28, 66.45, 127.56, 128.58, 139.11, 139.94; Anal. for $C_{17}H_{34}O_2Si$, Calcd: C, 68.39%, H, 11.48; found: C, 68.14%, H, 11.65%

Sulfide **160** was obtained from above alcohol as described for the preparation of compound **149**; 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.02 (6H, s), 0.85 (9H, s), 0.87 (3H, s), 1.17-1.97 (10H, m), 3.54 (2H, t), 3.7 (1H, m), 5.52 (2H, m); ^{13}C NMR ($CDCl_3$, 300 MHz) δ20.25, 20.32, 25.55, 25.98, 26.02, 26.89, 32.50, 33.64, 41.96, 42.30, 63.11, 124.78, 125.40, 126.53, 126.62, 128.76, 131.36, 139.52, 139.89.

Preparation of sulfone **161**.

A solution of **160** (0.95 g, 2.43 mmol) and Pyridine (1 mL) was treated at -40^{o}C with m-CPBA (1.91 g, 50-60%, 6.08 mmol), and the reaction mixture was allowed to warm to room temperature overnight. The resulting mixture was pumped in vacuo to remove pyridine. Purification by flash

chromatography provided sulfone **161** (0.62 g, 60.6%); 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.02 (6H, s), 0.85 (9H, s), 0.90 (3H, s), 0.98-1.55 (8H, m), 1.91 (2H, m), 3.51 (2H, m), 3.67 (1H, m), 5.7 (2H, m), 7.52 (3H, m), 7.82 (2H, m); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 19.98, 20.05, 25.93, 26.44, 33.40, 33.44, 41.08, 42.06, 62.91, 116.56, 128.78, 129.27, 129.31, 133.52, 144.65; Anal. for $C_{23}H_{38}O_3SiS$, Calcd: C, 65.35%, H, 9.06%; found: C, 65.24%, H, 9.21%.

Preparation of aldehyde **162**.

Deprotection of compound **161** as described for **84** to produced an alcohol, followed by oxidation as described for **138** to give aldehyde **162** as a colorless oil.

Alcohol (same as compound **163**): 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.91 (3H, s), 1.1-2.2 (11H, m), 3.59 (2H, m), 3.71 (1H, m), 5.75 (2H, m), 7.49-7.68 (3H, m), 7.88 (2H, m); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 19.45, 19.67, 24.06, 30.92, 33.33, 40.75, 41.19, 62.63, 116.59, 127.81, 128.84, 129.27, 133.57, 143.98.

Aldehyde **162**: 300 MHz ^{1}H NMR ($CDCl_3$) δ 0.72-2.15 (11H, m), 3.7 (2H, t), 5.77 (2H, m), 7.48-7.7 (3H, m), 7.88 (2H, m), 9.75 (1H, s); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 19.65, 19.88, 28.05, 28.71, 36.95, 43.16, 44.46, 121.99, 126.55, 128.79, 131.33, 135.98, 140.64, 202.14.

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BIOGRAPHICAL SKETCH

Yongping Xie was born in Lanzhou, China, in 1956. After graduating from Lanzhou Secondary High School in 1973, he spent almost three years as a farmer in Yuzhong County, Ganshou Province, and spent two years as an electrician in the Lanzhou Bus Company. In 1978 he enrolled in the Lanzhou University and received a B.S. in organic chemistry in July 1982. In August 1982, he became a research associate in Bee Research Institute of Chinese Academy of Agriculture, Beijing. In 1984 the Institute send him to Italy as a visiting scholar. He visited almost all major Italian cities for his program in ten months. In June, 1989, he arrived in the USA for a graduate program in chemistry. After obtaining an M.S. degree in organic chemistry at Wright State University in August 1991, he entered the Department of Chemistry at University of Florida. His Ph.D. in chemistry is expected in May, 1995. Upon completion, he will move to Purdue University in West Lafayette, Indiana, where he will work in the Department of Medicinal Chemistry and Pharmacognosy as a postdoctoral fellow.

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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